ATLAS OF THE BLOOD IN CHILDREN

LONDON
HUMPHREY MILFORD
OXFORD UNIVERSITY PRESS

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KENNETH D BLACKFAN, M D

Late Thomas Morgan Rotch Professor of Pediatrics Harvard Medical School
Late Physician in Chief Infants and Children's Hospitals Boston

LOUIS K DIAMOND, M D

Assistant Professor of Pediatrics Harvard Medical School Visiting Physician
and Hematologist Infants and Children's Hospitals Boston

WITH ILLUSTRATIONS BY

C MERRILL LEISTER, M D

Associate Pediatrician St Luke's Hospital Bethlehem and
Allentown General Hospital Allentown Pennsylvania

THE COMMONWEALTH FUND

NEW YORK 1944

FIRST PRINTING, DECEMBER, 1944
THIRD PRINTING, JUNE, 1946

PUBLISHED BY THE COMMONWEALTH FUND
41 EAST 57TH STREET, NEW YORK 22, N. Y.

PRINTED IN THE UNITED STATES OF AMERICA
BY A. HOEN & COMPANY, INC., BALTIMORE, MD.

Foreword

ILLUSTRATION is essential in hematology The inadequacy of language to convey the appearance of disease to the mind renders an appeal to the senses desirable whenever it can be employed, and when the objects themselves cannot be presented the best substitute for them is to be found in pictures Hematology is but a branch of general medicine, and physiology brings much of significance to it

Although the diagnosis of a blood disorder may sometimes be made from a study of the peripheral blood, very often the clinical manifestations of the patient together with a blood examination establish the diagnosis Diseases called blood diseases often affect quite other parts of the organism than the blood For example, gallstones may cause the presenting symptoms in a case of chronic hemolytic jaundice, and the earliest sign of acute leukemia may be arthralgia It is therefore entirely fitting that diseases of the blood be discussed by clinicians deeply interested in this subject rather than solely by men devoting much time to the laboratory aspects of the blood

There has always been need for pictures of the blood of children The child s blood shows much greater variation from normal than the adults The lability of children s blood is the rule In fact, in the infant the hematopoetic equilibrium is even less well established than in the child, and the younger the individual the greater the instability of the blood Leukocytosis may be more striking, nucleated red cells may appear where only polychromatophils would develop in an adult, and myelocytes and even myeloblasts may be found instead of the usual moderate shift to the left in adults Lymphocytosis develops with much greater ease in children and the blood platelets also may fluctuate with rapidity All these and other alterations of the three different formed elements of the blood make the diagnosis or the evaluation of the blood picture in a child more difficult

The fact that this is an atlas of the blood in children does not limit its usefulness to practitioners of pediatrics There is essentially no blood disorder in adults that is not seen in children except Addi-

sonian pernicious anemia However, the reaction of the blood in young individuals and in adults to the same stimuli is quite different A disease given the same name in children and in adults may present different blood pictures, and it is important that the differences be emphasized so that more accurate interpretation of the blood will be made in children

For many years the late Doctor Blackfan and his associate, Doctor Diamond, studied the blood extensively and both have been unusually well qualified to discuss it Doctor Blackfan always emphasized in his teaching the need for good illustrations of the blood cells Doctor Leister, a rare combination of pediatrician and artist, made it possible for the authors to accumulate splendid, accurate paintings of the blood for the use of students and practitioners of medicine

It was the happiness of patients that Doctor Blackfan felt came first of all His keen interest in the blood arose from his conviction that it required years of mature experience to treat the individual patient with a blood disorder no matter what the laboratory examinations did or did not show from a hematologic standpoint However, his real sympathy and concern for the patient never interfered with his determination to gain all possible information about the underlying disease

Tremendous perseverance on Doctor Blackfan's part led to the accumulation of all the knowledge so well illustrated and concisely stated in this *Atlas of the Blood in Children* His untimely death on November 29, 1941, deprived us of a master pediatrician and a great teacher

GEORGE R MINOT, M D

March 1944

Preface

IN 1925, a few years after he came to Boston as medical chief of the Infants and Children s Hospitals, the late Dr Kenneth D Blackfan became interested in the large number of patients seen in these hospitals who presented disorders of the blood In 1927 we established a hematology laboratory wherein such patients might be studied more carefully Since that time, observations have been recorded on more than five thousand infants and children, many of whom have been followed for several years, throughout the course of their illnesses This opportunity for long time personal observation has led to a wider knowledge of many diseases, particularly with regard to individual variations in reaction, changing symptoms, course, prognosis, and effective therapy

From the outset we planned to study not only the specific blood diseases but also deviations from the normal in either numbers or types of blood cells We were constantly impressed with the importance of considering the clinical manifestations exhibited by the patient as well as the morphological changes in the blood Consideration of either alone is not always sufficient to guarantee a clear understanding of the nature of the disease In fact, serious error may occasionally result from overemphasis on one feature to the exclusion of the other This is well exemplified in the difficulty often encountered in the diagnosis of leukemia At times the only evidence of this primary blood dyscrasia may be found in clinical manifestations, the blood cells showing relatively little alteration On the other hand, there may be no objective symptoms of ill health although examination of the blood yields clear-cut evidence of a malignant disease process And again, the changes discernible both by physical examination and by blood studies may be so indefinite that only the careful interrelation of all the findings suggests the presence of this disease

With such problems in mind we recorded for each patient the clinical data obtained from detailed histories—the symptoms at onset as well as those occurring during the progress of the disease the essential

findings on physical examination, on first admission, and throughout the course, and notes as to therapy, both successful and futile The information so secured was correlated with hematologic and other laboratory data In addition, stained dry films of the blood were prepared, mounted on slides, and saved for a permanent collection, as *examples of the types of disturbance encountered*

It became apparent early in our studies that for purposes of instruction illustrations of characteristic types of cells would be of greater value to medical students and physicians than a collection of stained films We were indeed fortunate in obtaining the aid of Dr C M Leister In him are combined a student s keen interest in hematology and an artist s ability to portray accurately what he sees Through his efforts a series of paintings of blood cells seen in many of the disturbances of the blood in childhood were prepared The plates so produced were supplemented with brief descriptions and discussions *of disease entities and are here reproduced in the form of an Atlas of the Blood in Children*

It has not been our purpose to include all the blood disorders that may be seen in childhood This treatise is restricted entirely to conditions with which we have had close personal experience, and for this reason diseases uncommon in this locality have been omitted

In the preparation of the illustrations, blood films were chosen from verified cases of each condition These films were drawn on cover slips from drops of blood obtained from the earlobe, the finger, or the toe, after drying they were stained with Wright s stain Where reticulocytes were sought, *the blood was drawn on cover slips previously* stained with brilliant cresyl blue, dried, and counter-stained with Wright s stain Representative fields, *as observed under the micro scope*, were reproduced as accurately as possible In only a few instances were selected cells from several fields combined in a single plate

A method of classification and presentation of the plates has been adopted which should assist in the rapid identification of the cells commonly occurring in the peripheral blood of infants and children with a given disease For example, the student may select the predominating type or the characteristic cell in a stained dry film of the blood, by comparison with the plates presenting like features, he may

reach a correct diagnosis of the disease, in so far as this can be done by examination of the blood alone

The text of the *Atlas* has been made as brief as possible For those seeking a more comprehensive and more detailed discussion of any of the diseases here presented, a short bibliography is appended to serve as the basis for further reading

Dr Blackfan always believed and taught that in the treatment of disease the care of the individual patient should not be forgotten This cannot be emphasized too strongly in the management of children It is therefore suggested that the student read carefully and take to heart the brief chapter on 'Care of the Patient

We are indebted to the members of the Resident Staff of the Infants and Children's Hospitals for their assistance, to Dr Sidney Farber for his aid in interpretation of histological data, and to Miss Geneva Daland of the Thorndike Memorial Laboratory of the Boston City Hospital for her valuable criticism of details of cell morphology

Finally, it is a pleasure to express our appreciation and gratitude to the Commonwealth Fund for the constant assistance and support which alone made possible the excellent reproduction of the plates and the publication of this *Atlas*

L K D

May 1944

Care of the Patient

It is not our purpose to discuss in detail the treatment of the many complaints which need to be and can be alleviated during the course of a given disease, but rather to re emphasize the fact that there are certain principles of general care which may be applied to all diseases

The old adage treat the individual, not the disease is particularly applicable to the care of ill children, because they differ so widely in their reaction to specific disturbances and in their response to the various measures of therapy Of course, specific therapeutic agents should be used promptly but never to the exclusion of the many little things which are of unquestionable value during the course of an acute or a chronic illness, through convalescence, and up until the time of complete recovery

Rest in bed or a regime of regulated restricted activity according to the individual circumstances, freedom from overfatigue and worry, comforting and intelligent nursing care, pleasurable occupational entertainment, and attention to the calls of nature are essentials of the first rank The diet should be arranged according to the individual s needs and desires, restricting food when necessary and increasing food when advisable, but always having in view the need to maintain a proper water balance with palatable, satisfying fluids and a sufficient caloric intake and an abundance of vitamins, thus avoiding dehydration, loss of weight, and the development of deficiency diseases The self-selective diet plan for children is admirable and often well tolerated, providing it offers a well-balanced menu Temperature, humidity, and ventilation with prevention of drafts should be adjusted to assure comfort to each patient Exposure to infection should be strictly avoided Daily baths and other hygienic measures must not be neglected

Specifically acting drugs that afford relief from many of the associated minor complaints arising in children with disorders of the blood should be used freely For instance, there is morphine for pain,

salicylates for fever and for aching muscles and joints, codeine for cough, sedatives for insomnia, and innumerable other medications, each of which finds a useful place in rendering comfort to the suffering child

Truly successful and thorough treatment demands that we consider in each case not only the specific remedy for the disease, but also the numerous adjuncts which experience has taught us will permit the patient to enjoy the greatest degree of comfort and happiness throughout his illness

KENNETH D BLACKFAN, M D

February 1941

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I. The Blood Cells

BREVITY in description of the diseases of the blood in infants and children will be facilitated by a preliminary review of the morphological varieties of the blood cells and their origin and by a statement of the nomenclature which will be used. It will also be helpful to bring clearly into view the differences between blood formation in early life and in the adult, and the features of change in the blood cell picture throughout the growth period.

In the description offered here as to the origin, development, and terminology of the cells of the blood, the polyphyletic theory of Sabin and her associates has been followed. This theory proposes a separate parent cell, derived from the reticulo endothelium, for each of the adult cells; that is, a megaloblast for erythrocytes, a myeloblast for granulocytes, a lymphoblast for lymphocytes, and a monoblast for monocytes. A primitive undifferentiated cell may intervene between the fixed reticular cell and the free parent cell. In normal states, the type of cell produced depends upon the site of origin; that is, granular leukocytes (neutrophils, eosinophils, and basophils) arise from the reticulum in the bone marrow, lymphocytes from the reticulum in the lymphoid tissue, and monocytes from the reticulum in the connective tissue of the spleen and other organs. On the other hand, in disease states the reticulum in any tissue may give rise to a specialized type of cell. For example, in certain pathologic processes such as tuberculosis, Sabin and her associates have followed the development of monocytes from reticular cells in the bone marrow and have stimulated such unusual leukogenesis experimentally by the injection of large numbers of tubercle bacilli or products of the organism. Normally, however, each cell seems to have its own site of origin, its own parent stem cell, and its own regular method of maturation. The development of the different types of cells in the blood, according to this concept, is illustrated in Charts 1, 2, 3, and 4.

The red blood cells arise from the endothelium in the bone marrow by way of a primitive red cell (Chart 1). The earliest recognizable

form is called the *megaloblast*. This cell has intense basophilia in the cytoplasm and an irregular arrangement of chromatin in the nucleus. The megaloblast matures through the *erythroblast* stage, during which the basophilia gradually diminishes and hemoglobin staining begins to appear in the cytoplasm, the nucleus becomes more condensed and stains more deeply. The next step in maturation is the *normoblast*, the basophilia of the cytoplasm has almost completely disappeared and the hemoglobin has reached its normal content. The nucleus is pyknotic and is extruded either as a whole or in fragments. Occasional small fragments, termed *Howell-Jolly bodies*, may remain in the cell. After the extrusion of the nucleus, the faintly basophilic erythrocyte filled with hemoglobin is called a *polychromatocyte* or *polychromatophilic erythrocyte*. When stained with brilliant cresyl blue, this basophilic substance may be seen as a mass of bluish filament or occasionally punctate staining material which gives the name of *reticulocyte* or *reticulated erythrocyte* to the cell. Finally, after the basophilia has completely disappeared the cell has become a *normocyte* or *mature erythrocyte*. One other evidence of immaturity in the erythrocyte is the presence of a *Cabot ring body*. Normally, maturation through the polychromatocyte or reticulocyte stage takes place in the bone marrow and the cell is then delivered to the peripheral blood. In disease states, however, erythrocytes in all stages of immaturity, even cells as primitive as the megaloblast, may be found in the peripheral blood.

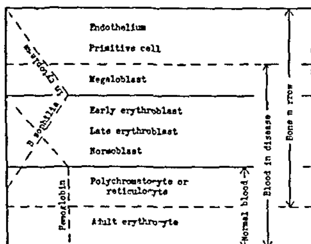


CHART I Maturation in erythrocyte series

In different disease conditions the size or the shape or the hemoglobin content of the erythrocyte may be altered. Various terms are used to designate the type of cell so produced, for instance, *macrocyte*, meaning a cell larger than normal, *microcyte*, meaning a cell

smaller than normal, *poikilocyte*, meaning an oddly shaped cell, *hyperchromic erythrocyte*, meaning a cell appearing to be too well filled with hemoglobin, *hypochromic erythrocyte*, meaning a cell deficient in hemoglobin, *spherocyte*, meaning a spheroidal-shaped cell in contrast to the biconcave shape of the normal erythrocyte, and *sickle cell*, meaning one that has assumed a sickled form Examples of these cells are shown in Plate 1

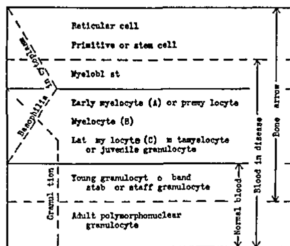


CHART 2 Maturation in myeloid series

The earliest recognizable cell of the myeloid series is the *myeloblast*, which arises from a primitive free cell derived from the reticular tissue in the bone marrow (Chart 2) The myeloblast has nucleoli in the nucleus and intense basophilia in the cytoplasm, both of which disappear as the cell matures The next step in maturation is the *myelocyte*, called A, B, and C by Sabin to indicate increasing maturity Gradually, as the basophilic cytoplasm dimin ishes, nuclear material becomes condensed and distinctive granulation appears in the cytoplasm, at which time the cell is known as the *metamyelocyte* The transition phases in the process of maturing are shown in Plate 2 At maturity, when the full complement of either neutrophilic, eosinophilic, or basophilic specific granulation has been deposited in the cytoplasm and the segmentation of the nucleus into two or more lobes has been accomplished, the mature forms of *polymorphonuclear leukocytes* are reached Ordinarily it is only these ma ture forms that are delivered to the peripheral blood, but in disease states immature forms even as primitive as myeloblasts may appear Plate 3 shows these cells

The *lymphocyte* is derived from a primitive free cell arising from reticular tissue in the lymphoid system (Chart 3) The earliest recog nizable form is the *lymphoblast* with scant, deeply basophilic cyto

plasm and a nucleus that often contains nucleoli In the process of maturation the basophilia in the cytoplasm diminishes, and with the formation of a more condensed nucleus the basophilic *young lymphocyte* is formed Further diminution in the basophilia in the cytoplasm and condensation of the nucleus result in a cell containing a relatively large amount of cytoplasm, this cell is termed a *large lymphocyte* Further decrease in size produces the *medium lymphocyte* The most mature form is the *small lymphocyte*, in this cell the nucleus is condensed and the cytoplasm, which is usually clear blue and contains no basophilia, is scanty Reddish granules occasionally appear in the cytoplasm of this cell Normally cells in the last four stages appear in the peripheral blood, but in disease states even lymphoblasts may be found The various stages of maturation of the lymphocyte are shown in Plate 4

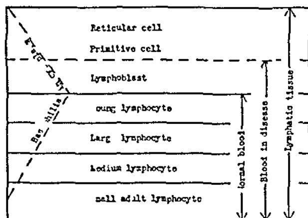


Chart 3 Maturation in lymphoid series

The *monocyte* originates from a primitive cell derived from the reticular tissue or connective tissue in the lymph nodes and spleen (Chart 4) This primitive free cell gives rise to the *monoblast*, the earliest recognizable cell of this series The cytoplasm is scant and moderately basophilic and the large nucleus contains nucleoli In the process of maturation, the basophilia gradually disappears and the nucleus becomes somewhat more condensed The *mature monocyte* has a nucleus which is often kidney shaped or somewhat folded on itself, and the cytoplasm may contain bluish red granules, particularly at the periphery Only two forms, young monocytes and adult monocytes, normally appear in the peripheral blood, in disease states monoblasts also may be found The cells in the monocyte series are shown in Plate 5

In certain pathologic states, especially in bacteremia, a type of mononuclear cell which is actively phagocytic may be found free in

the circulating blood This cell is spoken of as the *mononuclear phagocyte, endothelial leukocyte,* or *clasmatocyte* According to Sabin and other writers it is derived from the endothelial lining of the blood capillaries The cell is much larger than the normal monocyte The nucleus is eccentrically placed and lightly stained The cytoplasm, which is faintly granular, usually has one or more vacuoles which may contain ingested protoplasmic material Examples of these cells are shown in Plate 5

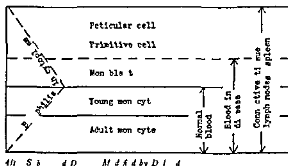


CHART 4 Maturation in monocyte series

In addition to the cellular elements mentioned above, *thrombocytes* are found in the blood It is generally agreed that they arise from *megakaryocytes*, giant cells found in the bone marrow These cells have one or more large round, irregularly staining nuclei and a granular, ill defined cytoplasm which often shows long protoplasmic processes These processes break off and subdivide and appear either singly or in masses as the *platelets* in the circulating blood (See Plate 5)

Inasmuch as the blood during infancy and childhood differs so materially in many respects from that during later life, it is not always possible to secure the maximum diagnostic aid from the stained blood film unless the peculiarities at different age periods are clearly recognized The particular features of note are (1) the more wide spread distribution in early life of the blood forming tissues, (2) the variation in the number and in the types of the formed elements in the blood and blood forming tissues at different ages, and (3) the unusual response of the hematopoietic system in infancy and childhood to differing stimuli Knowledge of these factors is essential for an accurate diagnosis

In the embryo, blood cells arise from the mesenchymal tissues, the first to form being the erythrocytes This process begins in the body stalk and the more general connective tissues then involves in turn the liver, the spleen, the lymph nodes, and finally the bone marrow

The leukocytes originate in the same organs but at a later period of embryonic life Prenatally the liver and spleen are the seats of active hematopoiesis and these organs attain their maximum function in this respect during the last two months of gestation At birth, blood is formed primarily in the bone marrow, the process gradually becoming less active in the extramedullary sites With growth and development there is a gradual segregation and concentration of hematopoiesis in the marrow cavities of the long bones and flat bones, the

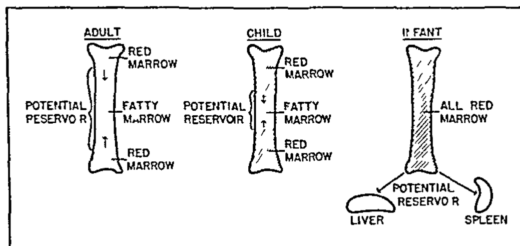


CHART 5 The active hematopoietic tissue and the potential reservoirs for conversion to this function normally found in adult child and infant

exception to this being normal formation of lymphocytes and monocytes, which occurs throughout life in the lymph nodes and the spleen As the marrow space increases with body growth, there is further concentration of blood forming tissue toward the ends of the long bones, leaving yellow marrow in the mid shafts This stage is reached by about the seventh year of age and continues to adulthood, when only the metaphyseal ends of the long bones and certain flat bones show active production of blood cells The smaller potential reservoir of fatty marrow that can in case of need be converted into actively hematopoietic red marrow helps explain the more rapid development of anemia and its greater incidence in children and infants than in adults In infants practically no fatty marrow exists, so that increased need for blood cells readily stimulates extramedullary hematopoiesis in the liver and the spleen, causing rapid enlargement of these organs

Chart 5 is a diagrammatic comparison of hematopoiesis in the adult, the child and the infant

In case of severe drain on the blood-forming tissues, the yellow marrow may become red as a consequence of reversion to hematopoietic activity Doan has shown experimentally the steps by which marrow laden with fat cells is transformed into active marrow when there is an increased need for blood cells First, there is replacement of fatty tissue with gelatinous marrow next the formation of red blood cells, then finally of white blood cells

In the bone marrow of the newborn, erythroblasts and megaloblasts predominate, the normoblasts and reticulocytes characteristic of adult hematopoietic centers being relatively few in number A similar situation exists in the myeloid series of cells early myelocytes and myeloblasts are more numerous than late myelocytes and mature granulocytes With advancing age, there is an increasing number of mature forms In the interpretation of particular blood states in childhood, it is important to keep in mind the normal changes in the absolute and relative numbers of cells and the variation in form that take place from birth through adolescence

At birth there is a definite macrocytosis a tendency to polycythemia, and a relative polymorphonuclear leukocytosis The presence of immature erythrocytes—reticulocytes and nucleated red cells—as well as of occasional myelocytes is characteristic of the age (see Plate 6), by three to six months a slight hypochromic anemia with relative lymphocytosis has developed from the second year to adolescence there is a gradual change in the total number and in the percentage distribution of the various cell forms until the normal levels of adult life are reached A tabulation based upon the determinations of several investigators as well as on personal observations is shown on page 8 and a graphic representation of the changes in red cells and hemoglobin is shown in Chart 6

The morphologic characteristics of the blood cells in the young also vary with age At birth the leukocytes are uniformly of the young type, frequently immature Most of the polymorphonuclear cells have only two-lobed or three-lobed nuclei, many have unsegmented nuclei and show basophilia in the cytoplasm Infection or any other stimulus to blood production tends to call forth immature forms,

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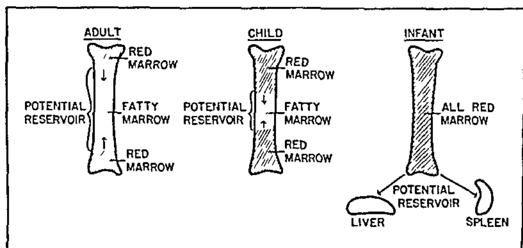


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AVERAGE NORMAL BLOOD VALUES AT DIFFERENT AGE LEVELS

	At birth	*At 2 days*	*At 14 days*	*At 3 months*	*At 6 months*	*At 1 year*	*At 2 years*	*At 4 years*	*At 8 12 years*
Red cells per cu mm (in millions)	5 1	5 3	5 0	4 3	4 6	4 7	4 8	4 8	5 1
Hemoglobin									
grams per 100 cc *	17 6	18 0	17 0	11 4	11 5	12 2	12 9	13 1	14 1
percentage of normal	113	115	109	73	74	78	83	84	90
White cells per cu mm (in thousands)	15 0	21 0	11 0	9 5	9 2	9 0	8 5	8 0	8 0
Platelets per cu mm (in thousands)	350 0	400 0	300 0	260 0	250 0	250 0	250 0	250 0	250 0
DIFFERENTIAL SMEARS PERCENTAGES									
Polymorphonuclear neutrophils	45	55	36	35	40	40	40	50	60
Eosinophils and basophils	3	5	3	3	3	2	2	2	2
Lymphocytes	30	20	53	55	51	53	50	40	30
Monocytes	12	15	8	7	6	5	9	8	8
Immature white cells	10	5							
Percentage of nucleated red cells in total nucleated cells	1–5	2							
Percentage of reticulocytes in total red cells	2	3	1	0 5	0 8	1	1	1	1

* Hemoglobin in whole blood value of 15 6 grams per 100 cc equivalent to 100 per cent

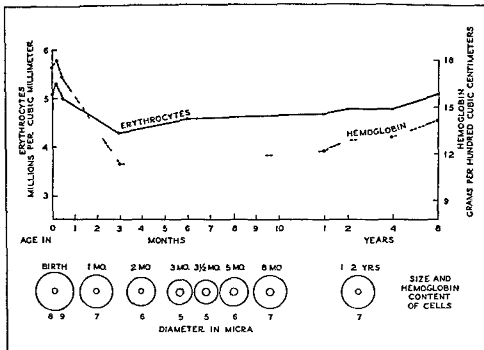


CHART 6 Normal values of erythrocytes and hemoglobin at different ages Note the relative polycythemia commonly found at birth and the relatively higher level of hemoglobin than of red cells This is explained by the fact that at birth the cells are macrocytic with the full complement of hemoglobin in each cell During the first two weeks there is a rapid fall in both erythrocyte and hemoglobin levels the erythrocytes gradually decrease in size with a more rapid diminution in hemoglobin content as depicted below the graph Between three and five months of age the erythrocytes are microcytic and hypochromic The blood improves slowly from the lowest level at the third month of life until the normal values for erythrocyte count cell size and hemoglobin content are reached between the first and second years

including myelocytes in great numbers The lymphocytes and the monocytes likewise show evidence of immaturity by the presence of abundant basophilic cytoplasm and large nuclei with occasional nucleoli

Immediately after birth, the erythrocytes are of the macrocytic type The cells are well filled with hemoglobin and show evidence of immaturity by the presence of reticulocytes, nuclear particles, and nucleated forms Within the first few weeks the macrocytes disappear and the normal sized erythrocytes (about 7 micra in diameter)

make their appearance By about the third month the hemoglobin level invariably has dropped but the erythrocytes have decreased relatively little in number During this transitional period, the red cells exhibit surprisingly little hypochromia, the result of a decrease in size of the cells which, however, remain relatively well filled with hemoglobin After the sixth month, the erythrocytes slowly increase again in size, the hemoglobin level rises, and a normocytosis returns (See Plate 6)

The response of the hematopoietic system to a specific demand for increased function is directly related to the age of the individual and the intensity and duration of the stimulus In the infant, the need for the formation of more blood results in a rapid reversal to the fetal form of hematopoietic activity, as has been diagrammatically illustrated in Chart 5 As evidence of this change, the lymph nodes, the spleen, and the liver may become demonstrably enlarged

Stimulation of hematopoietic activity by increased oxygen want, as occurs with anemia, infection, or other stimuli, results in a rapid drop in the proportion of mature to immature forms in the hematopoietic centers and in the ready appearance of younger cells in the peripheral blood Likewise, because of the limited reserve both of mature cells and of total hematopoietic tissue in the child in comparison with the adult, anemia will quickly develop as the result of a drain upon the blood-building system

II. The Erythrocytes in Anemia

For convenience in using the plates in this atlas, the anemias in infants and children have been grouped on a cytological basis as far as possible—that is, according to the size (normocytic, macrocytic, or microcytic) and hemoglobin content (normochromic, hyperchromic, or hypochromic) of the erythrocytes in each form Consideration of the cell types characteristic of each form permits classification into five groups, with an additional mixed group in which the striking feature is the accompanying jaundice There is, of course, some overlapping among the groups, especially in the last group

Normocytic normochromic anemia As the term implies, the erythrocytes are not altered in shape, size, or hemoglobin content The essential characteristic is a decrease in the number of red cells in the circulation, occasioned by failure on the part of the bone marrow to deliver adequate numbers of red cells to the peripheral blood Occasionally the marrow is hyperplastic In such instances a bone marrow block is said to exist, suggesting that there is interference either with the maturation of the cells or with the delivery of mature cells to the circulation Or the bone marrow may actually be depleted anatomically of its erythropoietic elements so that red cells are not being formed and the level of erythrocytes in the peripheral circulation consequently falls

If the anemia that results from either mechanism is associated with a deficiency in the other formed elements of the blood, the leukocytes and the thrombocytes, the condition is generally spoken of as *aplastic anemia* If the erythrocytes are diminished with little or no decrease in the number of leukocytes or thrombocytes, the term *hypoplastic anemia* has been applied, indicating that a less severe degree of bone marrow insufficiency exists affecting chiefly, but not solely, the erythrocytes This is generally considered a milder degree of derange

make their appearance By about the third month the hemoglobin level invariably has dropped but the erythrocytes have decreased relatively little in number During this transitional period, the red cells exhibit surprisingly little hypochromia, the result of a decrease in size of the cells which, however, remain relatively well filled with hemoglobin *After the sixth month, the erythrocytes slowly increase* again in size, the hemoglobin level rises, and a normocytosis returns (See Plate 6)

The response of the hematopoietic system to a specific demand for increased function is directly related to the age of the individual and the intensity and duration of the stimulus In the infant, the need for the formation of more blood results in a rapid reversal to the fetal form of hematopoietic activity, as has been diagrammatically illustrated in Chart 5 As evidence of this change, the lymph nodes, the spleen, and the liver may become demonstrably enlarged

Stimulation of hematopoietic activity by increased oxygen want, as occurs with anemia, infection, or other stimuli, results in a rapid drop in the proportion of mature to immature forms in the hemato poietic centers and in the ready appearance of younger cells in the peripheral blood Likewise, because of the limited reserve both of mature cells and of total hematopoietic tissue in the child in comparison with the adult, anemia will quickly develop as the result of a drain upon the blood-building system

II. The Erythrocytes in Anemia

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ment in the hematopoietic system which may progress to a severe aplastic anemia but is more likely to improve either spontaneously or after treatment. In this classification is placed an anemia of unknown etiology, *chronic hypoplastic anemia*. Another form is that occurring in prematurely born infants whose birth weight is less than five pounds or 2,250 grams; it is known as the *anemia of prematurity*. Finally, normocytic normochromic anemia is the immediate result of *acute blood loss*, such as occurs in hemophilia and in hemorrhagic disease of the newborn as well as in many other conditions associated with sudden and extensive hemorrhage; there is no change in the character of the cells but merely a decrease in number.

Macrocytic hyperchromic anemia. In this form the erythrocytes are larger than normal and yet are well filled with hemoglobin. However, the total number of cells per cubic millimeter of blood diminishes progressively as the condition continues. The bone marrow, although hyperplastic, fails to deliver cells in sufficient number to maintain the normal level in the peripheral circulation. The pathogenesis of this form of anemia is similar to that of Addisonian pernicious anemia in adults, but the primary etiologic factor of persistent achylia gastrica with lack of the intrinsic substance of Castle is seldom observed in childhood. The conditions associated with this form of anemia, which is relatively rare in children, are listed on page 39.

Macrocytic hypochromic anemia, that is, an anemia characterized by large cells deficient in hemoglobin, is seen only in the disease known as *Mediterranean anemia*. Although these large cells are far outnumbered by microcytic hypochromic cells in the blood of patients with this disease, the presence of even a few such cells suggests this diagnosis. This disease is described more fully below in the group of anemias characterized by jaundice.

Microcytic hypochromic anemia. In this condition the red cells are smaller than normal and are deficient in hemoglobin. This may result from a deficiency in iron or interference with its utilization which may be brought about by a number of factors; therefore this is commonly called secondary anemia. The most common of these causes are discussed on pages 42-44.

Microcytic normochromic anemia. In this condition the erythrocytes are small but relatively well filled with hemoglobin, and both

by actual measurements and by observation under the microscope the cells appear more nearly spherical than usual Such changes in the erythrocytes suggest hemolytic anemia, chiefly the congenital form Since the characteristic feature of this anemia is jaundice, it is described in the next group

Anemia often associated with jaundice In this group have been placed the anemias in which jaundice is a prominent feature, the cytology may be variable There is evidence of increased blood destruction, as well as a more rapid rate of regeneration of erythrocytes A more or less pronounced anemia develops from this increased and inadequately compensated destruction of red cells The group includes

a *Mediterranean anemia* Although the majority of the erythrocytes are microcytic hypochromic in type, the more characteristic feature is the presence of macrocytic hypochromic cells—large, thin, flat cells deficient in coloring matter, often with hemoglobin deposited in irregular clumps

b *Acute hemolytic anemia* The predominant red cell is well filled with hemoglobin and may be either normal in size or somewhat larger than normal Occasionally if the course is prolonged, microcytic globular erythrocytes appear Jaundice is invariably present and may be noted before pallor is apparent

c *Congenital hemolytic anemia* or chronic hereditary hemolytic jaundice This disease, in which recurrent jaundice and anemia are diagnostic features, is characterized by the presence of microcytic normochromic globular cells known as spherocytes

d *Sickle cell anemia* This disease occurs chiefly in Negroes The diagnostic feature is the presence in the peripheral blood of sickle shaped cells, especially if the blood is permitted to stand in an atmosphere of diminished oxygen tension

e *Erythroblastosis fetalis* or *hemolytic anemia of the newborn* This form of anemia is so frequently associated with jaundice that the diagnosis must be considered in any newborn infant who exhibits jaundice and anemia

THE NORMOCYTIC NORMOCHROMIC ANEMIAS

As previously indicated, under this heading are discussed the following conditions

- Aplastic anemia
- Congenital hypoplastic anemia
- Anemia of prematurity
- Anemia of acute hemorrhage, including hemophilia and hemorrhagic disease of the newborn

Aplastic Anemia

Aplastic anemia is the term applied to a normocytic normochromic anemia due to the failure of the hematopoietic system to deliver adequate numbers of red cells, white cells, and platelets to the peripheral circulation This results in profound anemia, leukopenia, and thrombocytopenia

The name indicates that the bone marrow has become histologically deficient in functioning tissue and, therefore, no longer supplies mature cells to the blood stream—that it has become aplastic This is not always strictly true as it not only is possible, but has actually been proved in many instances, that the bone marrow is macroscopically normal in appearance but physiologically inactive The net result, as far as the production of normal cells for the circulation is concerned, is similar to that found in an anatomically aplastic bone marrow *In such instances, a bone marrow block is said to exist*

It is necessary to appreciate that red-cell-producing tissue is present in many of the bones in the body Not all the hematopoietic tissue so widely placed is necessarily in the same state of anatomic and physiologic activity at the same time It is possible, therefore, to find active hyperplastic red marrow substance in one bone and relatively inactive hypoplastic tissue in another All stages of anatomic and physiologic activity may exist in various parts of the body and only when the production of cells becomes grossly deficient will the signs of aplastic anemia develop In the profound chronic states of aplasia, the greatest part of the hematopoietic system shows deficient cell-producing elements But all stages in this end picture

may be found in different patients, at different periods of the disease, and in different sites of hematopoiesis investigated

Aplastic anemia may result from toxins of either exogenous or endogenous origin, from severe nutritional deficiencies, from mechanical damage by x-ray radiation or radioactive substances, and from encroachment on the marrow tissue by metastatic tumors such as neuroblastoma and sarcoma, and primary tumors such as leukemia The anemia that results from any of these underlying causes of marrow insufficiency is termed secondary aplastic anemia Of the exogenous toxins, benzol and its derivatives, so frequently used in industrial processes, are the most common offenders Arsphenamine and other therapeutic agents that contain the benzol ring may produce similar disturbing effects

For those cases in which no discoverable cause for the abnormality in the hematopoietic system is revealed, the term idiopathic aplastic anemia is reserved This occurs more frequently in the child than in the infant However, when the manifestations appear shortly after birth it is called congenital aplastic anemia

Symptoms and Signs The onset is insidious Increasing pallor, anorexia, weakness, sleeplessness, and fatigue may appear singly or be noted as simultaneously present Palpitation and dyspnea with the development of hemic murmurs are associated with severe stages of anemia Frequently hemorrhagic phenomena, such as purpuric spots and ecchymoses and free bleeding from the nose or mouth, may precede these symptoms Occasionally in association with leukopenia, ulcerations appear in the mouth progressing to extensive stomatitis and even noma Lymphadenopathy and splenomegaly are not found as a rule

Laboratory Data The peripheral blood is characterized by a decrease in the numbers of granulocytes, thrombocytes, and erythrocytes, with a parallel fall in hemoglobin, producing a color index of unity It is not uncommon to find the number of red cells as low as 800,000 per cubic millimeter with 2 5 grams per cent of hemoglobin * The erythrocytes appear entirely normal in size, shape, and hemo

*The writers have seen children who with levels of 500 000 erythrocytes per cubic millimeter and 1 5 grams of hemoglobin were surprisingly comfortable and exhibited no clinical signs of cardiac distress

globin content The absence of polychromatophilic cells, reticulocytes, and nucleated erythrocytes indicates failure of regeneration Of the leukocytes the granulocyte series is most depressed, leading to a relative lymphocytosis Myeloid cells may be entirely absent The platelets likewise are diminished though a rare thrombocyte of an unusually large type may be found (See Plate 7)

Bleeding time is prolonged, retraction of the clot is delayed, but coagulation time is normal The fragility of erythrocytes in hypotonic saline solutions is normal The concentration of bilirubin in the blood serum is normal

There is no increase in excretion of urobilinogen in urine or feces

Diagnosis Profound anemia, leukopenia, and thrombocytopenia, with absence of young forms of erythrocytes and leukocytes, are indicative of aplastic anemia The secondary forms must be excluded since only in this way is it possible to avoid overlooking a specific form of therapy The presence of immature leukocytes suggests leukemia in a leukopenic stage, this may be a difficult diagnosis to establish without histologic examination of bone marrow

Course and Prognosis From its onset this form of anemia is rapidly progressive Either spontaneously or following some form of therapy a remission occasionally occurs Unfortunately this may be of only limited duration Following transfusion the patient may be greatly improved, but as the infused cells slowly degenerate, symptoms referable to developing anemia reappear in a few weeks Hemorrhage from the nose, mouth, or gums may hasten the diminution in erythrocyte level Borrowed blood' becomes less and less effective, transfusions being required progressively more often Recurrent blood loss and terminal infection of the upper and lower respiratory tracts generally lead to a fatal outcome

The high percentage of fatal cases makes the prognosis grave But it is impossible to predict in which patient and under what circumstances a spontaneous remission may occur A most promising suggestion for future investigation concerns the study of porphryn metabolism and its role in blood production The possibility has been suggested that an abnormality of this pigment metabolism may lead to an aplastic anemia, and correction of the abnormality may permit of normal blood production

Treatment Since adequate therapy is dependent upon the discovery of the causative factor, treatment must remain entirely symptomatic and of only temporary benefit Transfusion is indicated in sufficient amount and frequency to maintain a comfortable blood level and prevent hemorrhage Stimulants to hematopoiesis may be tried in addition to transfusion These include preparations of liver, both by mouth and parenterally, nucleotide and other nucleic acid products, bone marrow extracts, and dietary measures, particularly high vitamin preparations Roentgen-ray therapy over the long bones has occasionally stimulated hematopoiesis in the type of anemia associated with hyperplastic marrow tissue, but it should be avoided when the anemia is associated with an aplastic marrow The distinction should be made by biopsy before treatment is begun In severe aplastic anemia, therapeutic measures have been of little avail, and treatment by transfusion is the one palliative measure that may be depended upon

Splenectomy has been advised as a method of stimulating bone marrow production of erythrocytes, leukocytes, and thrombocytes, on only theoretical and experimental grounds Occasional instances of remission, either temporary or permanent, have been reported following this operation However, this drastic mode of therapy should be reserved for patients who have shown no response to medical treatment and for whom repeated transfusion may be difficult or unsatisfactory

CASE RECORD IDIOPATHIC APLASTIC ANEMIA

An eight year old white female child was admitted to the hospital because of pallor of two years duration There had been no other individuals with a similar complaint in the large family to which she belonged The birth and the health throughout infancy had been normal in every respect It was stated that she had always seemed slightly more pale than her brothers and sisters but never sufficiently so to require medical attention

At the age of six years the child began to bruise easily and had a tendency to bleed, especially from the nose At this time marked pallor was noted by her family and occasionally there was dyspnea on exertion but no interference with appetite satisfactory growth or gain in weight

Three months before entry, at the age of seven years and nine months examination of the blood had revealed anemia For this she was given

iron and liver medication without apparent effect Two weeks before entry there had been severe epistaxis on two occasions and the pallor of the skin and mucous membranes had become more profound

Physical examination revealed a well-developed and well nourished girl with marked pallor of the lips and mucous membranes and petechiae and ecchymoses about the hips and on the extremities There was no icterus although the skin seemed generally of a dark brown greyish hue The lymph nodes, the liver, and the spleen were not enlarged to palpation The area of cardiac dullness extended 3 centimeters beyond the nipple line on the left, there was a loud systolic murmur heard best at the apex, and a gallop rhythm

Examination of the blood revealed an erythrocyte level of 1,200,000 per cubic millimeter and a hemoglobin level of 3 2 grams per hundred cubic centimeters of blood, or 23 per cent The leukocytes numbered 2,400 per cubic millimeter and the platelets 33,000 Smears of the blood showed normal appearing leukocytes except for a decrease in neutrophils to 20 per cent The reticulocytes were 1 5 per cent of the erythrocytes, which were all normocytic and normochromic

During the following fifteen months the patient was admitted to the hospital on eleven separate occasions because of increasing pallor and frequent profuse epistaxes as well as bleeding from the gums and occasionally from the gastro intestinal tract Transfusion was given in amounts sufficient to improve the blood levels, but the beneficial effect seldom lasted more than five to six weeks Bone marrow biopsy revealed a generalized aplasia of all the cellular elements with replacement by fatty tissue The blood constantly showed a lowering of the erythrocyte and hemoglobin levels, as well as leukopenia and thrombocytopenia with prolongation of the bleeding time

When the patient was nine years and three months of age, she had a severe hemorrhage from the nose which could not be stopped even with local packing Transfusion was given repeatedly, but bleeding continued from the nose and from the gastro intestinal tract until death occurred

Comment This exemplifies a case of aplastic anemia of at least two years duration Frequently the history suggests that the condition may have been present for many years as in this instance in which the patient was said to have been pale since early infancy However, the symptoms of acute anemia and thrombocytopenia often are fairly recent in development As the anemia progresses, dyspnea and interference with activity may become troublesome However, as occurred here, an acute blood loss resulting from severe epistaxis precipitated the symptoms of blood want Examination of the blood reveals profound normocytic normochromic anemia with associated leukopenia and thrombocytopenia

When, as in this child examination of the bone marrow discloses an extremely hypoplastic or aplastic state, the prognosis must be regarded as grave Transfusion may be used as frequently as is necessary to improve the blood levels and control hemorrhage Occasionally such procedure is followed by spontaneous remission with rapid improvement in marrow regeneration More commonly, however, the anemia recurs relatively rapidly and if it is aggravated by frequent or constant bleeding even transfusion may produce little or no benefit and the patient may succumb from continued blood loss

Chronic Hypoplastic Anemia

Hypoplastic anemia is a normocytic normochromic anemia which differs from aplastic anemia in that it involves chiefly a failure of red blood cell production without as much depression of the leukocyte or platelet elements Although eventually it may be proved to be an earlier phase in the development of the completely aplastic picture, the patients so far studied have shown so distinctive a course that the condition deserves independent classification and description

General Considerations Isolated instances of this type of anemia have been observed in several clinics throughout the country, and five cases have been studied by us

The anemia has usually developed within the first three months of life and is therefore deemed to be congenital There has been no familial incidence, and no association with other types of anemia in members of the family Children of both sexes have been affected

No known cause has been discovered in any of the patients so far observed A history of infection, either in the patient or in the mother during gestation, has not been obtained In addition, contrary to the usual expectation, infection has not been prevalent to a greater degree in patients with this disease than in children with normal blood levels throughout similar periods of life There has been no evidence pointing to abnormality of the endocrine glands or to alterations in any of the other regional systems of the body

Presumptive evidence from present investigations favors the theory that this anemia may be associated with an inborn error in metabolism of the pigment or substances concerned in erythropoietic activity, or an early exhaustion of erythropoietic tissue

Symptoms and Signs The onset is insidious with a slowly developing pallor during the first few months of life When this pallor has progressed to a readily noticeable degree, lack of appetite, fussiness, and sleeplessness are noted in the infant Dyspnea and palpitation are present as the anemia becomes profound Purpuric spots, ecchymoses, and free bleeding do not appear during the course, which in our patients has extended over many years

With transfusion the symptoms abate, only to recur after six to eight weeks as the number of erythrocytes and the hemoglobin concentration fall to their previous low levels Enlargement of the heart and loud hemic murmurs are notable at the time of profound anemia, but these signs disappear when the red cell values are raised to within normal limits as the result of transfusion

It is truly remarkable, in so severe an anemia as these children repeatedly exhibit, how little the growth and development are affected With the exception of the need for repeated transfusions, they may lead active and happy lives

After transfusions have been repeated for many years, the skin may show pigmentation suggestive of mild hemochromatosis, the liver may become enlarged, and other evidences of increased pigment storage, such as enlargement of the spleen and lymph nodes, may be detectable The degree of such changes has been directly related to the amount and frequency of blood injection

Laboratory Data The erythrocytes are of the normocytic normochromic type but are reduced in number, the count in some instances being less than 1,000,000 per cubic millimeter The hemoglobin value is proportional to the number of red cells Reticulocytes are generally present but only to the extent of about one to two per cent, indicating an attempted regeneration, insufficient in degree The leukocytes usually are slightly diminished in number, averaging around 4,000 to 5,000 per cubic millimeter with relative neutropenia However, a leukocytosis develops as a response to infection, demonstrating the ability of the bone marrow to react to such a specific stimulus The platelets, as a rule, are normal or only slightly reduced in number (See Plate 8)

The bleeding time, the clotting time, and the clot retraction are within the normal range The fragility of the erythrocytes in hypo

tonic saline solutions is normal An increase in the icterus index is not demonstrable

Diagnosis A progressive anemia without significant diminution in the leukocytes or the platelets, beginning within the first three months of life and not related to either acute or chronic infection, is suggestive of this disease

If, in association with a hypoplastic anemia, immature leukocytes appear in the peripheral blood or a persistent thrombocytopenia develops, the diagnosis should be questioned If doubt exists, a study of sections from the bone marrow is indicated Bone marrow biopsy repeated at intervals has shown a hypoplastic state with immaturity of cells of both series as a conspicuous feature The difference between this bone marrow picture and that in aplastic anemia is one of degree only

Course and Prognosis Of our first five patients, two had spontaneous remissions one a year after splenectomy, so that the value of this procedure could not be definitely judged (see Chart 7), the other, without specific therapy at the age of three years One patient after seven years of repeated transfusions succumbed to a fulminating pneumococcus septicemia, at post mortem examination the bone marrow showed slight aplasia, and the other organs, in addition to evidences of infection present terminally, showed only the changes resulting from repeated transfusions, that is, great hemosiderin deposits Two patients continued to require transfusions at about eight-week intervals and had neither improved nor retrogressed through the many years they were followed At eleven, the oldest patient was fully developed and normal in every respect except for recurring anemia

The prognosis must be guarded until the children now under observation have been followed for a longer time It may be said, however, that with repeated transfusions these patients have maintained normal growth and development and such good health that therapy is indicated only according to the response of the individual

Treatment Transfusions of suitably matched* whole blood have

* The development of atypical agglutinins in the recipient from the use of donor s blood containing agglutinogens not present in the patient such as the Rh factor must be rigidly prevented lest the infused blood be destroyed rapidly or even cause serious transfusion reactions

been the only effective therapy to date These have been given at intervals of eight to ten weeks or whenever the patient's blood level reached about 1,500,000 erythrocytes per cubic millimeter From recent experience it would seem a better policy to offer smaller amounts of blood, that is, 100 to 200 cubic centimeters, at more frequent intervals, in an effort to maintain the level of erythrocytes and hemoglobin more constantly at a better functional state, thus lessening the degree of blood destruction and the deposits of pigment in the tissues which follow the frequent injection of larger amounts

Preparations of liver either alone or combined with iron and given either by mouth or parenterally, bone marrow and bone marrow extracts, vitamins in large amounts, and transfusions of blood plasma have all been administered to these patients without any beneficial effect However, the need for a well-balanced diet should not be overlooked while treating the patient with specific hematopoietic substances

As mentioned above, splenectomy has been carried out without striking benefit, but so limited an experience does not permit the drawing of any definite conclusions as to the value of this procedure

CASE RECORD CONGENITAL HYPOPLASTIC ANEMIA

A five month old white female infant was brought to the hospital because of pallor, beginning shortly after birth The father and mother were living and well and knew of no anemia or blood disease in any other member of the family One older child was in good health and had no symptoms of anemia The infant had been born at term by normal delivery Pallor had been noted, however, before discharge from the hospital at two weeks of age, and the baby had been given a transfusion During the following two months there had been a recurrence of pallor of the lips and mucous membranes, coming on gradually There was no jaundice the child nursed well and gained weight satisfactorily At the age of two months and three weeks the erythrocyte level was found to be 1,000,000 per cubic millimeter, and she was transfused once more at the hospital of her birth Iron sulfate was then given orally in addition to the breast feeding but the erythrocyte level gradually decreased during the ensuing two months

Physical examination at five months of age showed a well developed and well nourished infant with marked pallor of the skin, lips, and mucous membranes There was no variation from normal, except for enlargement of the heart and a systolic murmur heard best at the apex, and palpable liver and

spleen at the costal margin Petechiae and ecchymoses and icterus were not present

Laboratory data showed an erythrocyte level at this time of 1,200 000 per cubic millimeter, and hemoglobin of 3 7 grams per hundred cubic centimeters of blood (22 per cent) The leukocytes numbered 4 600 per cubic millimeter, and the blood platelets 200 000 Stained smears of the blood showed normocytic normochromic erythrocytes The leukocytes were normal in type and percentage distribution The reticulocytes numbered one per cent Examination of the urine and the feces revealed no abnormality and no evidence of increased blood destruction Tuberculin and Hinton tests were negative

There was no evidence of infection during the course of her hospitalization and the patient seemed entirely well Three transfusions of matched whole blood were given within five days with a subsequent rise in erythrocyte level to 4,500,000 per cubic millimeter and hemoglobin to 13 grams

Following discharge from the hospital, the patient continued to gain and grow well and appeared normal except for increasing pallor and fall in erythrocyte level to 1,000,000 per cubic millimeter and hemoglobin to 3 5 grams or 20 per cent Transfusion was given at intervals of two months or whenever this low level of erythrocytes and hemoglobin was reached and the patient was discharged each time very much improved There was never evidence of increased destruction of blood the administration of iron in large doses by mouth and of liver extract both by mouth and parenterally failed to increase the reticulocyte level, which constantly remained at one per cent or less

Biopsy of sternal bone marrow revealed a moderate increase in the amount of fatty cells and a decrease in hematopoietic tissue for the age, the depletion affecting the erythrogenic elements more than the leukogenic elements The megakaryocytes were normal in number

One year after first admission to the hospital splenectomy was performed in the hope of effecting an improvement in hematopoietic activity Examination of the spleen revealed enlargement of this organ to two and one half times the normal size for the age with slight fibrosis and hemosiderosis present diffusely through the tissues

Following operation the child continued to require transfusion, but at increasingly longer intervals for the following eight months

At the age of twenty five months two months after a transfusion, the erythrocyte level was found to have fallen only to 2,500 000 per cubic millimeter from a previous value (after transfusion) of 4,000,000 The reticulocytes at this time numbered over 2 per cent Thereafter there was no further diminution in the levels of the blood At three years of age the patient s erythrocyte count was 2,600 000 per cubic millimeter and hemo

been the only effective therapy to date These have been given at intervals of eight to ten weeks or whenever the patient's blood level reached about 1,500,000 erythrocytes per cubic millimeter From recent experience it would seem a better policy to offer smaller amounts of blood, that is, 100 to 200 cubic centimeters, at more frequent intervals, in an effort to maintain the level of erythrocytes and hemoglobin more constantly at a better functional state, thus lessening the degree of blood destruction and the deposits of pigment in the tissues which follow the frequent injection of larger amounts

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no further diminution in their number There was gradual improvement during the following twenty months which permitted the patient to continue normal activity with no further dependence upon infused blood (See Chart 7)

Although splenectomy is only rarely followed by a remission such as this in patients with hypoplastic anemia or even aplastic anemia, such operative interference may be worthy of trial, especially if transfusion becomes difficult to administer or if the patient shows increasing bone marrow aplasia

Anemia of Prematurity

In an infant born prematurely there takes place, during the first three months of life, a rapid decrease in the number of red blood cells and an even more rapid diminution in the hemoglobin content This constitutes the anemia of prematurity

General Considerations Several explanations have been advanced to account for this condition It was at one time believed that the anemia was caused by a deficiency in the storage of iron resulting from the shorter period of intra-uterine life However, actual measurements of the iron concentration in the liver and other viscera of premature infants have failed to demonstrate a poverty in this element Also, the administration of iron during the development of the anemia has not proved to be an effective measure in limiting the degree of anemia

It is now generally thought, although proof is wanting, that the same mechanism as that which influences the development of physiological anemia in the full term infant is responsible In other words, the polycythemia of the newborn infant appears to be the result of oxygen unsaturation of the fetus in utero, and the transition to a higher oxygen tension after birth may be an influencing factor in the disintegration of the erythrocytes and in the reduction of the excess concentration of hemoglobin Other alterations in the blood at this time that may have a bearing on the production of the anemia are the larger number of immature erythrocytes and possibly an embryonal type of hemoglobin

There is need to take into consideration the fact that the premature infant grows at a relatively faster rate than the full-term infant and that, consequently, a greater demand for blood is placed on the more

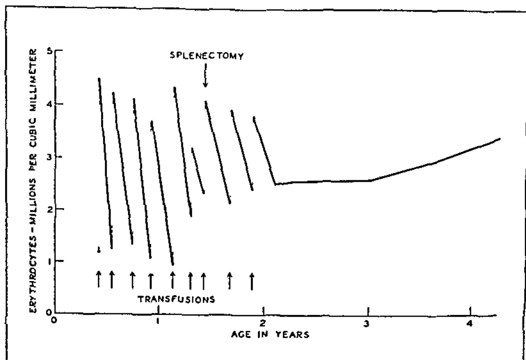


CHART 7 Hypoplastic anemia This child, first admitted at about five months of age required transfusion approximately every two months for a year in order to maintain life Note the immediate rise in erythrocyte level after each transfusion Following splenectomy transfusions were required less frequently, the last one was given at the age of twenty three months At about age two a spontaneous though slow improvement in erythrocyte and hemoglobin levels began By the fourth year the red cells had reached about 3 000,000 per cubic millimeter

globin was 8 4 grams At three years and eight months the erythrocyte level was 3,000,000 per cubic millimeter and hemoglobin was 8 8 grams (See Chart 7) The patient s growth, activity, and general behavior were entirely normal for the age

Comment In this five-month old infant the diagnosis of hypoplastic anemia was suggested by the failure in regeneration of the erythrocytes without comparable diminution in the levels of leukocytes and platelets *Bone marrow biopsy confirmed this diagnosis Since no treatment other* than transfusion at six to eight-week intervals produced any improvement in the number of erythrocytes or the concentration of hemoglobin, splenectomy was performed in an effort to improve the erythrogenic activity of the bone marrow tissue There was slow but definite increase in red blood cell production thereafter as evidenced by the longer intervals between the necessary transfusions Eight months after splenectomy the erythrocytes became stabilized at a level of 2,500,000 per cubic millimeter and there was

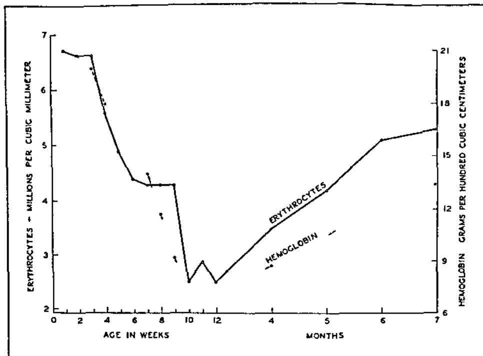


CHART 8 Anemia of prematurity Erythrocyte and hemoglobin levels of an infant born two months before term He weighed two pounds and twelve ounces at birth and his length was sixteen and a half inches Note the rapid fall in blood levels to the tenth to twelfth week then spontaneous recovery in the ensuing four months The hemoglobin concentration lagged behind the erythrocyte count during this recovery period

being inversely proportional to the birth weight of the infant For example, an infant having a birth weight of four pounds (1,800 grams) would have about 3,500 000 erythrocytes per cubic millimeter and 10 grams of hemoglobin per 100 cubic centimeters of blood (about 60 per cent) at three months, whereas an infant with a birth weight of two pounds (900 grams) would show about 2,500 000 erythrocytes and 7 5 grams (45 per cent) of hemoglobin Reticulocytes are relatively scarce in the stained smears

After the twelfth week the erythrocytes increase steadily in number until by the seventh month the figures normal for that age in full-term children are attained—about 4,700,000 per cubic millimeter At the twelfth week the hemoglobin concentration is always lower, proportionately, than the number of erythrocytes Thereafter, it rises

immature and probably less actively functioning hematopoietic system Also, with a smaller total volume of blood at birth there is necessarily a limited supply of substances re-utilized for hemoglobin formation

This anemia is a characteristic of all immature infants Its severity is inversely proportional to the state of maturity, which may be roughly evaluated by the weight of the infant at birth In a premature infant weighing five pounds (2,250 grams), the number of red cells and the hemoglobin concentration are not altered to the same degree as in one weighing less Usually, by the third month of life a gradual spontaneous improvement begins, as evidenced by the rise in the number of erythrocytes and an increase in the hemoglobin content, by the seventh month normal values are reached In our series of cases this feature has been observed even in infants weighing as little as two pounds (900 grams), providing there is a steady gain in weight Nutritional disturbances and an inadequate diet, infections, and congenital anomalies interfering with orderly growth and development may result in a prolongation of the anemia into the latter part of the first year or even into the second year of life

Symptoms and Signs Attention is first attracted to the development of anemia during the second month after birth, when the normal rosy hue of the skin and mucous membranes is replaced by a gradually increasing pallor which reaches its greatest severity at the end of the third month From this time on, the pallor gradually becomes less apparent until about seven months of age when the skin and mucous membranes appear normal in color The appetite remains unimpaired, physical activity is unaltered, the temperature reaction is stabilized, and the stools are not changed in color or consistency as the anemia appears and recedes The superficial lymph nodes and the liver are not noticeably enlarged The spleen may become palpable, possibly as the result of extramedullary hematopoietic activity It recedes about the eighth month of life There is no indication of a bleeding tendency

Laboratory Data The blood is characterized by a simultaneous fall in number of erythrocytes and in hemoglobin level, beginning shortly after birth and continuing until the tenth or twelfth week At this time the greatest severity in anemia is reached, the degree

number and type except for a relative lymphocytosis Occasionally there is a leukopenia which extends from the second to the fifth month

The platelets are not altered in number or character, and no abnormality in bleeding or clotting time or in the fragility of the erythrocytes in hypotonic saline solutions has been noted

Diagnosis The diagnosis is made by the finding of an anemia varying with the age of the premature infant and reaching its greatest degree of severity at the end of the third month Immature cells of the erythrocyte series are rarely found in the stained smears The hemoglobin content is lower than the number of erythrocytes after the third month of life This form of anemia is to be distinguished from that resulting from acute pyogenic infections, syphilis, congenital and malignant diseases of the blood

Course and Prognosis The course is self limited Recovery is spontaneous with increasing maturity of physiologic function, and by the seventh month the recovery of the healthy, normal premature infant is complete Superimposed infection, inadequate diet, and other etiologic causes may prolong the course beyond the usual period of recovery

Treatment Therapeutic efforts to improve or halt the development of the physiological anemia of prematurity within the first three months for the most part have been unsuccessful However, some writers believe that early treatment with anti anemic measures (iron with and without copper, liver extracts, sunlight, vitamins, etc ,) does lessen the degree of the anemia, but in view of the natural tendency for spontaneous recovery, further evidence as to the effectiveness of blood building substances is needed

After the third month and during the recovery period, since the hemoglobin lags behind the erythrocytes, it may be of value to give one of the available preparations of iron Ferrous sulfate in doses of two to four grains daily is suggested Thereafter the diet should be regulated according to the nutritional requirements of the patient

It is not our practice to resort to the transfusion of whole blood as a measure directed toward improvement of the anemia alone It is seldom necessary, except in the presence of complications, and at best its effect upon the blood is transitory

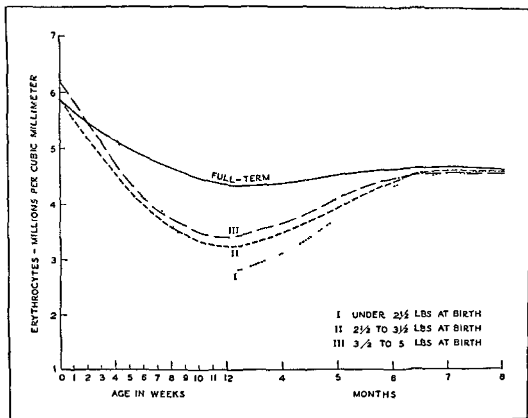


CHART 9 Anemia of prematurity, composite graphs of 75 prematurely born infants divided into three groups according to birth weight In the prematurely born infant the fall in erythrocyte level during the first three months is much greater than the normal physiologic anemia of the full term infant The anemia is directly related to the degree of prematurity or immaturity of the infant which is roughly proportional to the weight or length at birth, the smallest infants develop the most profound anemia The lowest level is reached by about the third month, and improvement thereafter produces a return to normal levels by the seventh to eighth month if the infant is otherwise well

much more slowly than the erythrocyte count These changes are graphically illustrated in Charts 8 and 9

In the initial period of the development of the anemia of prematurity little or no change from the normal is present in the cellular characteristics of the erythrocytes, but as the red cells begin to increase in number and the lag in the recovery of the hemoglobin content continues, hypochromic red cells with a tendency to microcytosis make their appearance

The leukocytes usually follow the normal variation for age in

Anemia of Acute Hemorrhage

The two most common diseases in childhood in which acute hemorrhage occurs are hemophilia and hemorrhagic disease of the newborn

Hemophilia

Hemophilia is a hemorrhagic disease of constitutional origin, usually familial, limited to the male but transmitted through the female It is characterized by a delay in coagulation of the blood and is associated with a tendency to bleed, especially after trauma

General Considerations Hemophilia was known in Biblical times, since the ritual of circumcision for newborn male infants was prone to disclose such an underlying bleeding trait It has been accurately reported in medical literature since the middle ages even the hereditary aspects were well recognized before the nineteenth century Although 90 per cent of the cases occur in the Caucasian race, the disease has also been observed in Negroes

The hereditary considerations are important True hemophilia occurs only in the male It follows the Mendelian law and is an example of the inheritance of a sex-linked recessive character The females who transmit the disease are known as carriers

Many theories have been advanced as to the cause of the retardation in the formation of the clot in hemophilia In severe cases the clot may fail to form, but in the majority of patients coagulation takes place eventually with the elaboration of a normal amount of fibrin Some writers suggest that there is a delay in formation of thrombin but the cause of this abnormality is not known Other observers state that neither a deficiency in prothrombin nor an increase in antithrombin has been demonstrated, and that the platelets, which show no alteration in number or size, are excessively stable and fail to induce clotting of the blood The absence of a component of the plasma, as yet unidentified, has also been mentioned as a possible cause of the prolonged coagulation time

Symptoms and Signs The chief characteristics of hemophilia are a tendency to uncontrollable bleeding after the slightest trauma, spontaneous small hemorrhages, and bleeding into the joints This bleeding tendency may be present from birth It may be detected

CASE RECORD ANEMIA OF PREMATURITY

A white male infant was brought to the premature nursery at the Infants Hospital at the age of eight hours, after having been born at home by normal delivery in the eighth month of gestation There had been no difficulty in initiating respiration and no cyanosis

The physical examination revealed a small, immature appearing infant, whose color was good and whose breathing was normal The weight was two pounds and six ounces and the length sixteen inches

The infant was given breast milk by gavage for the first five weeks of life, at four hour intervals There was slow but steady gain in weight and regular growth in length After the fifth week, whole milk modification was gradually substituted for the breast feedings At the sixth week of life there was slight pallor of the skin and of the lips This increased slowly until marked pallor was evident, which reached its greatest severity at three months of age, when the weight was six pounds At this time the erythrocyte level was 2,800,000 per cubic millimeter, and the hemoglobin measured 8 4 grams per 100 cubic centimeters of blood, or 54 per cent The infant was discharged from the hospital At home he was given whole milk modification, Vitamin C in the form of ascorbic acid (25 milligrams daily), and Vitamins A and D in concentrate form in the necessary amounts Two grains of elixir of ferrous sulfate were given by mouth each day This medication was well tolerated

During the following three months the patient was seen biweekly, he exhibited normal activity, continued satisfactory gain in weight and a gradual improvement in color consistent with the increase in erythrocytes and hemoglobin which was noted At four months the erythrocytes numbered 3,500,000 per cubic millimeter and the hemoglobin was estimated as 9 grams per 100 cubic centimeters of blood, or 58 per cent At five months of age the counts were 4,050,000 erythrocytes and hemoglobin 10 grams, or 64 per cent, at six months there were 4,500,000 erythrocytes and hemoglobin 11 4 grams

Comment This case illustrates the usual anemia of prematurity which develops in an infant born before term with a birth weight of less than five pounds The greatest severity of the anemia was seen in this infant at three months of age, and thereafter there was regular improvement in the number of erythrocytes and in the hemoglobin concentration until these values reached almost normal levels after the sixth month of life During the height of the anemia there were no symptoms of blood want, and even without corrective measures the patient continued gaining in weight and growing at a normal rate Iron medication was given orally to increase the hemoglobin, which ordinarily tends to lag behind the erythrocyte level during the period of improvement

retraction is likewise normal after the clot has formed The capillary resistance test is negative

Roentgenograms, particularly of the joints, may show areas of calcification, and after repeated bleeding there are evidences of bone and joint destruction

Diagnosis The diagnosis of hemophilia is readily established on the basis of the following salient features history of the hereditary trait which although essential is not always obtainable, onset of the bleeding tendency shortly after birth or within the first few years of life, occurrence from time to time of severe and frequently uncontrollable hemorrhages, occurrence of hemarthrosis, and prolongation of the clotting time If the clotting time is close to the upper limits of normal it is important to repeat the test, especially during periods when hemorrhages occur

Primary and secondary thrombocytopenic purpura may be differentiated from hemophilia by a diminution in the number of platelets and the prolongation of the bleeding time Purpura unassociated with thrombocytopenia may offer difficulty in diagnosis, but the clotting time, carefully determined at several examinations, assists in distinguishing hemophilia from purpura

Course and Prognosis Hemophilia may begin in infancy and continue throughout life The course is variable and is influenced by the frequency and duration of the hemorrhage and by the amount of blood lost In the milder forms very little interference with growth and development or with normal activity is noticed In the more severe forms the dangers of prolonged and fatal hemorrhages are great, especially in the first and second years of life

The care of the child with hemophilia presents many serious problems Trauma, infections, and dentition cause considerable anxiety *Acute surgical emergencies are usually fraught with danger* Bleeding into the joints may so interfere with motion that permanent contractures result and produce crippling deformities There is no doubt that with increasing age the hemorrhages become less severe and less frequent and the chance of survival increases Resort to frequent transfusions has been instrumental in prolonging life and has undoubtedly lessened the mortality in this disease

Treatment The prophylactic treatment of hemophilia is of great

first after ligation of the cord, after ritual circumcision, or after any slight injury Even with no manifestations of free bleeding in the first eighteen months of life, ecchymoses may develop following everyday mild injuries when the child first learns to walk Intractable bleeding may be noted first following the removal of a loose deciduous tooth

Hemarthroses are common and more characteristic of this than of any other hemorrhagic disease Hemorrhage into the joint may result from the slightest trauma, the knee joint being most frequently involved and the elbow joint next The swelling may sometimes be enormous and may be associated with severe pain and some fever Limitation of motion may result After the hemorrhage has been absorbed, the same joint may again be the site of severe bleeding, finally leading to a permanent deformity from ankylosis or contractures

Pallor, weakness, dyspnea, and palpitation are directly related to the amount and rapidity of blood loss

Laboratory Data The erythrocytes are normal in size, shape, and hemoglobin content unless there has been severe or frequent loss of blood, in that event, mild or severe microcytic hypochromic anemia is present Following even a moderate hemorrhage, the reticulocytes may increase in number and nucleated erythrocytes may appear in the peripheral blood The leukocytes may also be somewhat increased after hemorrhage, with a relative increase in polymorphonuclear cells and in young forms of neutrophils The platelets are normal or increased in number (See Plate 9) In quiescent cases there should be no alteration in the number or in types of blood cells

The important finding is a prolongation of the clotting time In the normal individual the clotting time of blood from the capillaries is three minutes or less and of the venous blood seven minutes or less, whereas in hemophilia the clotting time is usually more than a half hour and it frequently is delayed for several hours It is important to note that variation occurs not only from one patient to another but also at different times in the same patient For this reason, a normal clotting time at a single examination is less conclusive as negative evidence than is a prolonged clotting time as positive evidence of the disease The bleeding time is normal and the

retraction is likewise normal after the clot has formed The capillary resistance test is negative

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Treatment The prophylactic treatment of hemophilia is of great

importance Patients should be restrained as much as possible in infancy and early childhood to prevent injury and accidents Strenuous exercise and participation in active sports should be avoided

Minor hemorrhages may be controlled by local pressure with hemostatic agents, especially serum of human and animal blood and tissue extracts Other methods of reducing the clotting time of the blood—for example, sensitization to a foreign protein such as horse or sheep serum or the use of fractions of human globulin—have been of value in individual cases These measures are transitory in effect, no therapeutic agents are as yet available to bring about permanent benefit

Major hemorrhages require transfusion It may be necessary to repeat this procedure several times before bleeding is controlled

Hemorrhagic Disease of the Newborn

The disease is characterized by bleeding unassociated with trauma or infection in infants during the first week of life A commonly used term is spontaneous hemorrhage in the newly born

General Considerations No clear line can be drawn between hemorrhagic disease of the newborn and hemorrhage following birth trauma or anoxia The opinion widely held at present is that in many instances slight trauma would cause no significant bleeding were it not for the underlying hemorrhagic tendency Serious injury at the time of delivery resulting in bleeding is not usually considered as part of this disease

Recent investigation has proved that the bleeding tendency is associated with a deficiency in prothrombin, that is, a hypoprothrombinemia The prothrombin content of the blood at birth is about one fourth of the adult value It falls somewhat lower in the first three days after birth and then rises slowly during the early months of life until normal values are reached by the end of the first year The peculiar susceptibility to bleeding between the third and the sixth day of life is dependent not only upon this lowered concentration of prothrombin in the blood, but also upon a contributing factor as yet obscure which interferes with the conversion of prothrombin into thrombin It has been shown that the available prothrombin falls sharply on the second day of life and does not return to the preceding value until after the fourth or fifth day The incidence of hemorrhage

can be closely related to the infant's prothrombin level and even more closely to that of the available prothrombin Spontaneous hemorrhages are likely to develop if the prothrombin is less than 10 per cent of the normal adult value

Prematurely born infants usually show lower levels of prothrombin than full term infants, and this fact may prove to be of importance in explaining the frequency of postnatal hemorrhages in premature infants

Symptoms and Signs The average time at which the hemorrhagic manifestations begin is about the third day after birth Rarely symptoms appear as early as twenty-four hours after birth or as late as the eighth day The duration of the bleeding tendency is seldom longer than three or four days and its cessation is often as abrupt as its onset

The hemorrhages are usually multiple Meningeal bleeding, though common, is usually so slight that it is not appreciated unless routine lumbar punctures are performed The hemorrhages most frequently recognized are those from the alimentary tract, the umbilicus, the skin, and the subcutaneous tissues Bleeding from the ears, nose, mouth, and genito-urinary tract is less frequent The bleeding usually begins insidiously, there being continual oozing rather than a gush of blood With increasing loss of blood, there may be prostration, tachycardia, and dyspnea Many of the symptoms depend on the site and the extent of the hemorrhage

Cutaneous hemorrhages often appear in places exposed to pressure, such as the occiput, the back, the sacrum, and the heels Persistent oozing from the umbilical stump despite re-tying of the ligature or application of a clamp is characteristic of hemorrhagic disease Extensive meningeal hemorrhage and serious internal hemorrhages into organs or serous cavities although comparatively rare have been demonstrated at necropsy Serious internal bleeding is usually accompanied by circulatory collapse This may denote extensive loss of blood into one of the body cavities, but an identical clinical picture may be caused by a smaller hemorrhage into the medullary portion of the adrenal gland

Laboratory Data The erythrocytes are lowered in number in direct relation to the amount of blood lost Since the normal level in the

first week of life is usually 5,000,000 per cubic millimeter or above, a fall to 4,000,000 red cells or less may be evidence of loss of blood The fall in hemoglobin concentration parallels the drop in erythrocytes In stained smears the erythrocytes show little or no alteration from normal, other than an increase in the numbers of reticulocytes and nucleated red cells

The leukocytes, which are commonly increased during the first three to four days after birth to levels of 15,000 per cubic millimeter or more, may show a further increase to 20,000 and even 30,000 The polymorphonuclear neutrophilic increase is relative and absolute in number and many immature forms of myeloid cells appear in the peripheral blood

The platelets are normal or may be increased in number to a level of 400,000 per cubic millimeter or more The bleeding time and the clotting time are usually not altered, but the prothrombin time as determined by the method of Warner, Brinkhouse, and Smith shows a marked increase The method of Quick, which measures both the prothrombin concentration and the "available prothrombin, always shows a marked fall in prothrombin levels to 25 per cent of normal or less

Diagnosis The recognition of external hemorrhage offers no difficulties, but symptoms of internal hemorrhage may be overlooked Occasionally the vomiting of blood in the first twenty-four hours may result not from a spontaneous bleeding but from the swallowing of bloody fluid during birth Spontaneous bleeding during the first week of life is nearly always due to hemorrhagic disease of the newborn and even in the presence of obvious trauma the possibility of this disturbance as an important contributory factor must be kept in mind Other causes of bleeding may occur at this age bleeding from the vagina alone may be due to pseudo-menstruation if the bleeding is confined to the nose and mouth, congenital syphilis must be suspected However, the onset of bleeding in the case of either syphilis or septic infection is usually later than the first week of life and is apt to persist even after specific therapy Traumatic delivery of the infant may in itself cause serious and extensive hemorrhage However, the underlying bleeding tendency may play an important role

Erythroblastosis fetalis in association with lowered platelet levels and prolonged bleeding time may cause hemorrhage, particularly in the first day of life This condition should be suspected if jaundice and profound anemia unrelated to obvious bleeding are present The diagnosis of erythroblastosis fetalis can be confirmed by the finding that the liver and spleen are enlarged and the level of nucleated erythrocytes is high

Congenital thrombocytopenic purpura may occur in the first week of life, although this is rare, the lowered platelet level or absence of platelets in smears of the peripheral blood associated with prolonged bleeding time should serve to differentiate this condition

Hemophilia may likewise occur at this early age, especially with trauma or surgical procedures such as circumcision, the prolonged clotting time and the history of the familial trait should serve to identify this condition

Course and Prognosis Hemorrhagic disease of the newborn is a self-limited condition The course is seldom longer than a few days, it is hardly ever protracted into the second week of life Once improvement begins, it continues rapidly, and relapses are uncommon At present the prognosis of hemorrhagic disease is formulated on the basis of experience before the advent of specific therapy Obviously, this will be altered, as it has already been altered greatly, by the ease with which specific therapy is now carried on and the widespread use of prophylactic treatment which serves to ameliorate, if not to prevent, the disease In the past the outcome was dependent upon the amount and the localization of the hemorrhage Of the cases with obvious hemorrhage in the brain or in the adrenal gland, more than 15 per cent terminated fatally Serious intracranial hemorrhage if not fatal may often result in physical incapacities or mental retardation

Treatment Hemorrhagic disease may now be regarded as a preventable disorder The effectiveness of Vitamin K given before delivery is well established Not only can spontaneous hemorrhage be practically eliminated by such a procedure, but statistics seem to indicate a reduction of hemorrhages formerly regarded as traumatic If Vitamin K is not given to the mother, it may be given effectively to the infant orally or parenterally

Transfusion is a procedure of established value in the presence of active bleeding Its effects are immediate, but it may require occasional repetition as the small amount of prothrombin supplied in the transfused blood persists in the circulation for only a few hours Fresh blood should be used in preference to stored blood, which is often low in prothrombin The amount of blood required is usually estimated on the basis of 5 to 10 cubic centimeters per pound of body weight Matched whole blood is preferable in order to avoid serious incompatibility even though the infant's serum may not be high in iso-agglutinin titer Intraperitoneal and intramuscular injection of blood should not be relied upon to check bleeding Although Vitamin K may replace transfusion as the common mode of therapy, the injection of blood is still necessary in the treatment of extensive bleeding, and the replacement of the blood lost often requires prompt attention In the event of serious loss of weight and in the presence of dehydration, the administration of normal salt solution subcutaneously and of 10 per cent solution of glucose intravenously constitutes a most important aid in treatment

THE MACROCYTIC HYPERCHROMIC ANEMIAS

As has been mentioned, the macrocytosis existing at the time of birth gradually disappears during the first month of life This macrocytosis is not associated with anemia and is not due to the lack *of the liver extract principle or of the erythrocyte maturation factor*, the deficiency associated with Addisonian pernicious anemia of adult life The existence of pernicious anemia in children has not been definitely proved by the presence of the criteria essential for the diagnosis of the disease in the adult, namely, absolute achlorhydria, recurrent glossitis, involvement of the spinal cord, and relapses after omission of liver treatment

However, pernicious-like anemia, implying a macrocytic anemia which may respond to liver extract principle, does occur in infancy and childhood and is due to a variety of causes other than permanent deficiency in the intrinsic substance of the stomach In the investigation of a macrocytic anemia in a child, a number of etiologic factors must be considered These are listed as follows

a Congenital malformations of the gastro-intestinal tract, leading to interference with the absorption of the liver extract principle This may produce a permanent deficiency requiring the constant administration of liver to the patient

b Acute or chronic disease of the gastro intestinal tract, interfering with the absorption of the liver extract principle

c Chronic intestinal indigestion or celiac disease which, although it is commonly associated with a microcytic hypochromic anemia, in a few rare instances has presented the characteristic picture of macrocytic anemia

d Postoperative shunts, by passing portions of the gastro-intestinal tract, in which the liver extract principle is either elaborated or absorbed, as may occur in operation for atresia of the small intestine

e Advanced cirrhosis of the liver, which interferes with the function of storage and synthesis and the release from the liver of hematopoietic material essential for erythrocyte maturation

f Rarely subacute or chronic leukemia, particularly when leukemic infiltration is widespread throughout the liver and the intestinal tract

g Tropical or non tropical sprue

h Acute infections in infants, with a temporary complete achlorhydria *

i Erythroblastosis fetalis or hemolytic anemia of the newborn

Macrocytic hyperchromic anemia due to any of the causes listed above except erythroblastosis fetalis may be described as follows

Symptoms The early manifestations, which may be found in anemia of any form, are anorexia, loss of weight, vomiting, and diarrhea Susceptibility to fatigue, lassitude, and sleeplessness are common in younger children

* The writers have observed fifteen infants between the ages of four and sixteen months in whom a severe macrocytic anemia developed and was corrected by the parenteral administration of liver extract In only one patient was more than one course of liver therapy needed The remaining children recovered completely after a single course of treatment

On physical examination, pallor of the skin and mucous membranes is observed The heart may be enlarged and hemic murmurs varying in intensity with the severity and duration of the anemia are likely to develop The liver is usually somewhat enlarged even in the absence of primary liver disease or leukemia The spleen likewise is enlarged The lymph nodes are not increased in size, except in the rare instance of macrocytic anemia associated with leukemia

Laboratory Data The degree of anemia is extremely variable The number of erythrocytes may be between 2,500,000 and 3,000,000 per cubic millimeter, whereas the hemoglobin may be reduced only to 10 grams, or 64 per cent * The color index is therefore high, usually being 1 3 or more The leukocytes are often elevated to between 10,000 and 25,000 per cubic millimeter and immature forms of poly morphonuclear neutrophils are present, occasionally, however, they are reduced with lymphocytes predominating The platelets are usually not affected, a bleeding tendency is present only rarely † (See Plates 10, 11 and 12)

Diagnosis The diagnosis is dependent upon accurate laboratory estimation of the erythrocyte and hemoglobin levels, as well as on the measurement of the cell size There are no symptoms peculiar to macrocytic anemia in childhood ‡ In each patient the underlying cause for the macrocytosis must be sought by exclusion of the various etiologic factors mentioned in the foregoing discussion

Course and Prognosis This varies with the underlying disease causing the macrocytic anemia In the presence of leukemia or of cirrhosis of the liver, a fatal termination is to be expected In malformations or disease of the gastro-intestinal tract, proper treatment of the underlying disturbance may shorten the duration of the anemia, the patient s eventual improvement being dependent upon the degree of restoration of normal function In the type of macro

* We observed one patient in whom the erythrocyte level was 600,000 per cubic *millimeter and the hemoglobin measured 3 3 grams or 21 per cent*

† In two of our patients there were associated thrombocytopenia and hemor rhagic manifestations in the skin and mucous membranes Following treatment this unusual complication disappeared

‡ In young infants with this condition curious protrusions of the fronto-parietal bones of the skull are occasionally seen

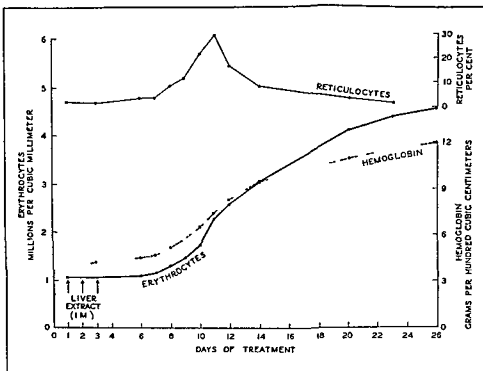


CHART 10 Profound macrocytic anemia following severe infection and complete achlorhydria Note that at entry reticulocytes were absent and that the hemoglobin level was relatively higher than the erythrocyte level Reticulocytes began to increase about four days after liver extract had been injected intramuscularly on three successive days and reached a height of about 25 per cent by the seventh day after the last treatment There was a proportionate rise in blood levels with a return to normal complement of hemoglobin in the normocytic red cells

cytic anemia associated with or dependent upon acute infection (see Chart 10), the course is generally of two to four months duration, especially if adequate specific therapy for both the anemia and the infectious process is instituted In most instances a relapse does not take place after the blood has reached normal levels

Treatment Therapy should be directed both to the correction of the underlying cause of the macrocytic anemia and to the prompt relief of the anemia In the presence of profound anemia, transfusion of matched whole blood should not be delayed since the response to liver extract may take two weeks or more As soon as the diagnosis has been made, specific treatment should be instituted,

consisting of the use of suitable preparations of liver extract or a comparable material such as ventriculin, in an amount sufficient to produce a maximum reticulocyte response The dosage varies with the individual patient Because of the difficulty of oral administration of these substances to small children, the preferable mode of therapy is parenteral injection of liver extract The dose of liver extract required is usually larger proportionately, considering the difference in weight, than that given the adult with pernicious anemia We have obtained a favorable response in children weighing twenty pounds with the injection of 10 cubic centimeters per week (equivalent to 1,000 grams of fresh liver) for a period of three weeks or more until the blood levels were restored to normal The amount and the frequency of administration must always be gauged by the reticulocyte response of each patient, which should reach a maximum within ten days, if this can be achieved without any untoward effect upon the patient

THE MICROCYTIC HYPOCHROMIC ANEMIAS

Microcytic hypochromic anemia results from a deficiency in or loss or poor utilization of the mineral iron necessary for the synthesis of the hemoglobin deposited in the red blood cells As the name indicates, the cells are smaller than normal and contain less hemoglobin pigment This condition is illustrated by Plates 18 through 23

The deficiency in iron may be brought about by a number of factors, the most common of which are described below

a *Acute or chronic infection* often interferes with the appetite and thereby diminishes the amount of iron containing food entering the body Likewise, during infection the absorption of the mineral from the intestinal tract has been shown to be faulty and the excretion of iron increased

b *Chronic bleeding* deprives the body of more or less of the iron which is ordinarily re-utilized after the break-down of hemoglobin Such blood loss and consequent iron loss from frequently recurring or constant small amounts of bleeding may quickly exhaust the stores of iron within the body and lead, therefore, to an iron deficiency anemia

c *Iron deficiency in the diet* is the simplest mechanism for the production of microcytic hypochromic anemia It is more likely to develop in infancy because the basic diet of the infant is milk which contains very little mineral iron If as iron containing foods are added to the diet the appetite fails or if the infant stubbornly refuses solid food, the negative iron balance usual during the first six months may be continued into the latter half of the first year or into the second year of life Also, comparatively larger amounts of iron are necessary per unit of body weight for the infant and the child than for the adult, because the process of growth and development necessitates iron for deposit in the cells of all tissues as well as for the building of muscle hemoglobin and blood hemoglobin

d *Anemia in the mother during gestation* may be reflected in the development of an iron deficiency state in the infant during the first six months of life During this period the infant is dependent upon stores of iron deposited before birth for the building of hemoglobin If the mother suffers from anemia dependent upon the inadequate ingestion or absorption of iron or iron-containing foods especially during the latter half of gestation, the deposit of iron stores in the body of the fetus becomes deficient Although this does not affect the level of erythrocytes or hemoglobin of the infant at the time of birth, such a deficiency manifests itself by the development of a microcytic hypochromic anemia in the untreated infant after the third month of life If the development of this anemia is anticipated or if medicinal iron or iron containing food is given in adequate amount when it is discovered, there is a prompt response on the part of the blood Likewise, if women during gestation are protected against the development of anemia or an established anemic state is improved by the administration of iron in adequate amounts, microcytic hypochromic anemia does not develop in the offspring This is illustrated in Chart 11

e *Twin or multiple births* may lead to the same deficit in iron stores in each infant as has been described immediately

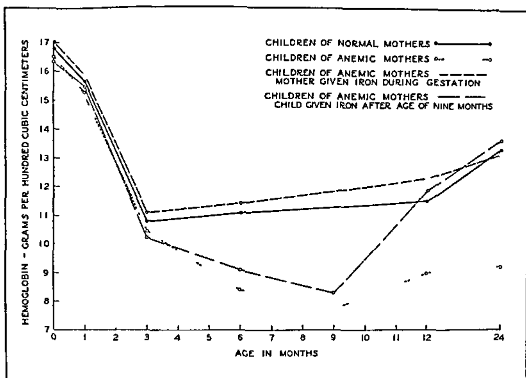


CHART 11 Anemia in children of anemic mothers composite graph of more than 50 children The blood of infants born to anemic mothers (commonly *with hypochromic anemia) is normal at birth During the first three months* there is the usual rapid fall in hemoglobin concentration that occurs in all infants In infants of untreated mothers the rise in hemoglobin during the ensuing months is slight due to a deficient prenatal storage of iron That this is a specific deficiency is indicated by the rapid response of the group of patients who were given medicinal iron from nine months of age An infant is protected against anemia if the mother is given sufficient amounts of iron during gestation

above Here again, large amounts of iron offered to the mother as prophylaxis during gestation will prevent the development of microcytic hypochromic anemia in such infants

f *Congestive splenomegaly*, with or without evidences of chronic or recurrent hemorrhage and usually dependent upon interference with the flow of blood from the spleen, resulting in congestion of this organ or in the splenic vein, is accompanied by this form of anemia

Iron Deficiency Anemia

This anemia is caused by the failure to receive or retain or properly to utilize iron in sufficient amounts to maintain the normal concentration of hemoglobin in the erythrocytes Synonyms in common use are dietary anemia, alimentary anemia, nutritional anemia, milk anemia, hypochromic anemia, secondary anemia, and chlorotic anemia of childhood

Etiology The lack of sufficient iron for hemoglobin formation is directly responsible for this type of anemia The factors leading to such iron deficiency have been mentioned above

Symptoms Although pallor of the skin and mucous membranes is usually the presenting symptom, frequently loss of appetite, irritability, fatigue, and weakness are associated with the anemia In cases of long standing there may be definite retardation in skeletal and muscular development The heart rate is usually increased and cardiac enlargement with easily audible murmurs is found Associated with the anorexia, a functional achlorhydria may exist Such children readily develop pica or abnormal appetite The spleen is slightly enlarged to palpation and the liver may likewise be enlarged

Laboratory Data In iron deficiency anemia the number of erythrocytes is disturbed relatively little at first, there being as a rule between 4,000,000 and 5,000,000 cells per cubic millimeter However, the hemoglobin content is low, ranging between 8 and 4 grams or 50 and 25 per cent, and the color index accordingly is less than one, often below 0 5 Microcytes containing very little hemoglobin pigment predominate in the peripheral blood The leukocytes are reduced and there is often a relative lymphocytosis The platelets are not altered in number, and a bleeding tendency is seldom observed

The course of the blood changes in a typical instance of iron deficiency anemia is illustrated graphically in Chart 12

Diagnosis The presence of a microcytic hypochromic anemia, with the number of erythrocytes around 4,000,000 or more per cubic millimeter and the hemoglobin concentration less than 10 grams per 100 cubic centimeters of blood (64 per cent), is characteristic of iron deficiency anemia The underlying cause of such deficiency must be sought in the history, the physical examination, and in the laboratory

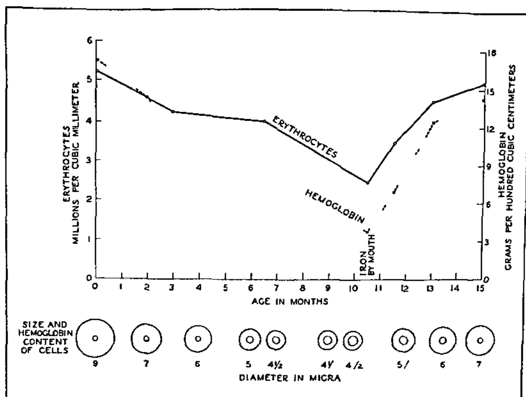


CHART 12 Iron deficiency anemia This patient suffered from anorexia and frequent vomiting from the fourth month of age Iron containing foods were offered but were taken poorly from the fifth month She was seen at infre quent visits treatment was ineffectual at home and a profound anemia had developed by the tenth month Note the gradual diminution in erythrocyte size and the relative hypochromia Following treatment with oral medicinal iron in effective dosage, there was rapid improvement in red cell numbers hemoglobin level, and size and hemoglobin content of the erythrocytes

data, including roentgenographic studies Only in this way can congenital malformations, acute or chronic infections, and other obscure causes for the iron deficit be disclosed Since iron deficiency anemia frequently exists in conjunction with vitamin deficiency diseases such as rickets and scurvy, the symptoms of the latter may often mask those dependent upon the anemia alone and may occasionally render the diagnosis uncertain

Course and Prognosis The course of iron deficiency anemia varies with the underlying cause and the treatment If hemorrhage or congenital malformation or infection is responsible for the anemic state, this must be remedied before medicinal or dietary therapy can

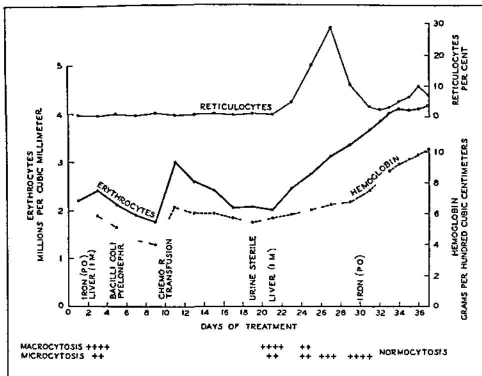


CHART 13 Anemia secondary to infection The smears of this patient s blood showed both macrocytic and microcytic hypochromic erythrocytes At the time of admission to the hospital the site of infection was not readily apparent, but on the fifth day of hospitalization cultures of the urine revealed a large number of colon bacilli causing pyelonephritis which was demonstrated to be secondary to congenital malformation in the genito-urinary tract While the infection was active treatment with iron by mouth and liver extract intra muscularly produced no increase in reticulocytes however after the infection had been successfully treated by chemotherapy and transfusion had been given resumption of therapy with liver extract intramuscularly on the twenty first day followed by medicinal iron orally on the thirtieth day produced specific improvement in the size of the blood cells and in erythrocyte and hemoglobin levels

be wholly effective For the simple iron deficiency state, the oral administration of iron leads to a prompt and satisfactory recovery Within two weeks the appetite improves At the optimum, the anemia is relieved at the rate of more than one per cent hemoglobin per day Complete cure may be expected in one to two months With specific therapy, the simple iron deficiency anemia dependent upon a low mineral intake should show rapid improvement However, the

presence of other deficiencies or of congenital malformation or of acute or chronic infections may alter this favorable outcome Danger exists chiefly from intercurrent infection which may lead to a fatal outcome As the result of infection, it is not uncommon to find a mixed type of anemia—that is, a combination of microcytosis and macrocytosis (see Chart 13)

Treatment The administration of iron, either medicinally or in a well-balanced diet, is specific for this form of anemia The response of the blood is similar to that following the treatment of pernicious anemia with liver extract After suitable amounts of iron have been given, a reticulocytosis occurs between the sixth and twelfth day from the start of treatment, and the blood levels improve thereafter Anorexia and irritability may disappear with amazing rapidity, and there is a steady improvement in the activity of the patient and an acceleration of normal growth and development

Relatively large doses of iron are indicated in childhood The present tendency is toward the use of ferrous sulfate in doses of six to twelve grains daily according to the age of the patient It has been found that the use of iron medication at meal times or in a milk diluent, as often administered to infants, is followed by a less satisfactory response both in reticulocytes and in the subsequent hemoglobin rise This seems to be the result of precipitation or combination of the iron with phosphate in the food, permitting smaller absorption of the mineral (see Chart 14) It is most noticeable when the iron is given in repeated small doses in milk It is therefore advisable to prescribe iron medication in a non-phosphate-containing diluent between meals

To facilitate a more rapid recovery, occasionally it has been advised that liver and aqueous liver extract be administered orally In the mixed types of anemia (i e, macrocytosis as well as microcytosis, as illustrated in Chart 13) parenteral liver extract therapy is indicated for most rapid improvement

Transfusion at the start of the treatment may shorten the period of recovery and improve the patient s general condition more promptly In fact, this method of increasing the blood levels may be the only satisfactory one when iron deficiency anemia is combined with or is due to acute or chronic infection, for with these complications the administration of iron may be ineffectual

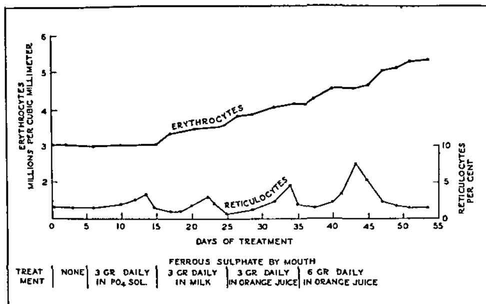


CHART 14 Effect of food on medicinal iron given at the same time After an initial control period of five days with no iron therapy a sub-optimal dose of ferrous sulphate was given by mouth in phosphate solution with very little reticulocyte response In the second period of ten days duration the same amount of medication given in milk produced only a slight reticulocyte increase and slight improvement in the erythrocyte level In the third period the same amount of iron given in orange juice (non phosphate containing diluent) produced a greater increase in reticulocytes which in the fourth period was proved to be the specific effect of the iron as an increased dose produced another reticulocytosis

CASE RECORD IRON DEFICIENCY ANEMIA

A white female infant was brought to the hospital at the age of eighteen months because of pallor from the fifth month of life Her mother had suffered from anemia both before and during her pregnancy and had been unable to tolerate iron medication which was prescribed in the latter months of gestation The patient was born at term and weighed seven pounds six ounces The color of the skin and mucous membranes was normal throughout the neonatal period Cow s milk modification was offered and well tolerated, and the patient gained satisfactorily for the first three months of life Orange juice was given at one month, and cod liver oil was added at two months and taken readily At four months of age the child s complexion became sallow and there was definite pallor of the lips and mucous membranes Egg yolk and cereal were offered at this time but refused by

the patient, consistently Vegetables and other soft solid foods were offered frequently during the ensuing three months but only milk was taken eagerly At six months the patient weighed sixteen pounds During the following eight months there was a gradual diminution in weight gain until an actual loss in weight occurred after one year of age, from a best weight of twenty pounds ten ounces to a weight at entry of nineteen pounds four ounces The pallor of the skin and mucous membranes continued, and the patient exhibited fatigue, irritability, and sleeplessness

On admission to the hospital the infant appeared pale and chronically ill Petechiae and ecchymoses were not present The heart was enlarged three centimeters beyond the nipple line, and there was a loud systolic murmur audible over the precordium, maximum at the apex The liver and the spleen extended two finger-breadths below the costal margin There was no enlargement of the peripheral lymph nodes

The erythrocytes numbered 3,350,000 per cubic millimeter and hemoglobin was 30 per cent or 4 7 grams per hundred cubic centimeters of blood The leukocyte level was 6,000 per cubic millimeter Differential blood smears showed a normal distribution of the various types of leukocytes with abundant platelets but predominantly microcytic hypochromic erythrocytes *Roentgenograms confirmed the enlargement in heart size and showed* diminution in growth of the skeletal bones The patient s urine and stools were entirely normal on laboratory examination The blood Hinton and tuberculin tests were negative Gastric analysis showed no free hydrochloric acid in the stomach contents and very little response to histamine injection

On the thirty fourth day of hospitalization the child was started on 6 grains of ferrous sulfate daily between meals in the form of elixir of ferrous sulfate divided into two doses per day On the seventh day *after this medi* cation was started, the reticulocytes rose from the previous level of one per cent to more than 10 per cent, and then rapidly diminished to a level of 4 per cent on the eleventh day after medication was started The erythrocytes and hemoglobin values rose rapidly, there being an increase of almost 2 per cent hemoglobin per day Smears of the blood showed increasing numbers of normal sized erythrocytes well filled with hemoglobin Concurrently the patient s appetite improved, *and she began to eat increasing amounts of the* soft solid foods offered

About two months after entry, at the time of discharge from the hospital, the erythrocyte level was 4,600,000 per cubic millimeter and the hemoglobin 11 grams per hundred cubic centimeters of blood or 71 per cent The cardiac murmur had disappeared The spleen and the liver were no longer palpable and the patient had gained eighteen ounces in weight Chart 15 is a graph *of the blood levels in this patient*

When seen two months later, the patient appeared entirely recovered, the

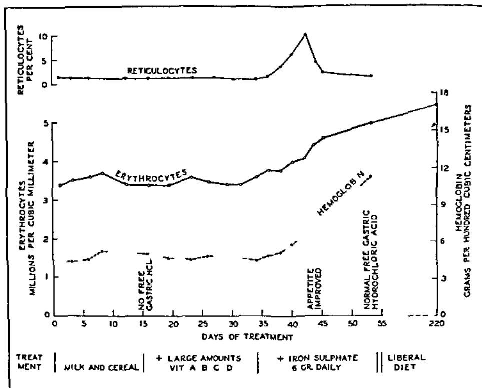


CHART 15 Iron deficiency anemia response to iron medication This patient eighteen months old had been on a diet deficient in iron and vitamins for a year At the end of an initial control period on the basic diet of milk and cereal gastric analysis showed no free hydrochloric acid There was no improvement when large amounts of vitamins were added to this diet but the further addition of ferrous sulphate by mouth was followed by a rise in reticulocytes and improvement in blood levels Improvement in appetite was almost as specific an evidence of response to proper therapy as was the reticulocytosis Note that gastric acidity was normal after successful treatment

erythrocyte and hemoglobin levels were normal for the age, and a generous varied diet was being taken

Comment This case is typical of the severe iron deficiency anemia which may result from deficiency in iron storage before birth caused by anemia in the mother during gestation as well as from a sub-optimal intake of iron containing food after the first six months of life As the anemia becomes more severe, there is further anorexia and frequently enlargement of the heart with loud murmurs which suggest congenital or acquired disease of the heart The blood shows typical microcytic hypochromic erythrocytes with a lowering of the hemoglobin level greater in degree than the diminu

tion in erythrocytes The gastric juice may be entirely lacking in free hydrochloric acid

Treatment with iron in sufficient dosage for the individual patient usually produces a marked reticulocytosis within seven to ten days after the beginning of the medication and a subsequent rapid rise in erythrocyte and hemoglobin values with the return of the erythrocytes to their normal size Frequently there is a marked improvement in the patient s appetite shortly after the reticulocytosis is found in the blood smears, and this materially increases the rate of recovery of the blood as well as improvement in the general condition and the growth and development of the patient The gastric juice, when retested after improvement has occurred, usually shows a return to its normal hydrochloric acid content

Splenomegaly with Anemia

Splenomegaly and anemia occur together commonly in infancy and childhood, and the underlying causes for their development are numerous and diversified Anemia in early infancy may be closely associated with an enlargement of the spleen as the result of extra medullary hematopoiesis During infancy and childhood many of the infectious disorders produce an anemia with splenomegaly Increased hemolytic activity, such as occurs in acute or chronic hemolytic jaundice, is invariably accompanied by splenomegaly as well as anemia Many forms of purpura are accompanied not only by anemia from blood loss but likewise by splenomegaly Anemia and splenomegaly are presenting symptoms in the congenital disturbance of blood formation such as Mediterranean anemia, sickle cell anemia, and erythroblastosis fetalis, in the malignant blood diseases such as lymphoblastoma and leukemia, and in diseases characterized by disturbances of lipid metabolism such as Gaucher's and Pick-Niemann s disease

In the past any discussion of the blood diseases in infancy has included a consideration of a symptom complex known as von Jaksch s anemia, or anemia infantum pseudoleukaemica This syndrome as originally described consisted of anemia, splenomegaly, and leukocytosis, with many immature red and white blood cells in the peripheral blood A specific etiologic agent common to all cases so classified has not been found, nor have characteristic histologic changes been

described for this form of anemia With the experience gained in recent years, the changes in the blood originally described by von Jaksch have been found to be the result of many different stimuli Therefore this term has been omitted from this *Atlas*

Congestive Splenomegaly

After all the above-mentioned causes for splenomegaly and anemia have been ruled out, there still remains a group of cases in which the symptoms have been found to result from interference with the venous return of blood from the spleen, resulting in congestion in this organ The manifestations of this condition have been described under a variety of terms such as Banti s disease or Banti s syndrome, splenomegaly with early gastric hemorrhage, thrombophlebitis of the portal and splenic veins, and splenic anemia These names have been applied to groups of symptoms and signs so dissimilar that it was difficult to explain them on a single pathologic basis

It is now generally accepted that congestion and stasis in the spleen produced either by some abnormality within this organ or in the spleno portal circulation may result in a symptom complex consisting of various degrees of splenomegaly, anemia, and associated disturbances The signs and symptoms produced are directly dependent on the site of the obstruction, the resulting alterations in the blood flow necessary to establish a collateral circulation, and the disturbances in function of the affected viscera, particularly the spleen Since the latter organ has an unexplained relationship to bone marrow activity, its altered function often results in anemia, leukopenia, and even thrombocytopenia

It is possible to recognize clinically and hematologically two distinct types of congestive splenomegaly which seem to merit independent description The first type is characterized by splenomegaly with early gastric hemorrhage resulting from spleno portal obstruction, the course and the symptoms, signs, and alterations in the blood depend on an obstruction in the portal or splenic system from either extrinsic or intrinsic factors, with the development of collateral circulation and the subsequent formation of esophageal and gastric

varices, the rupture of which accounts for the sudden profuse hemorrhage The causes for such obstruction may be hepatic disease, portal or splenic thrombophlebitis, pressure on the veins by enlarged lymph nodes, tumors, residual embryonic valves within the veins, or other unusual abnormalities

The second type of congestive splenomegaly cannot be related so directly to venous obstruction outside the spleen and may therefore result from disease processes within this organ It is characterized by enlargement of the spleen and the development of a microcytic hypochromic anemia with leukopenia and often thrombocytopenia

In addition to these two distinct types, patients have been observed who presented a combination of symptoms of an obstruction to the flow of blood through the portal and splenic veins, hemorrhage from ruptured varices, and microcytic hypochromic anemia with leukopenia and thrombocytopenia Since the clinical and hematological data in this latter group merge into the other types, it seems unnecessary to detail the salient features at this time

The two types of congestive splenomegaly in which the symptoms and laboratory findings appear distinct and characteristic are described below

Symptoms In the first type, the outstanding symptom is the sudden, unexpected occurrence of hematemesis in a child who previously had been in good health Examination of the abdomen immediately after the gastric hemorrhage usually reveals a spleen which is only slightly enlarged, if at all palpable After cessation of the bleeding, the spleen gradually enlarges and remains moderately enlarged until another attack of hematemesis occurs Sometimes after a duration of several years the spleen becomes constantly enlarged Examination of this organ shows an increase in size and a change in consistency Diffuse fibrosis, reduction in the red pulp, distension of sinuses, and compression of the Malpighian corpuscles, accompanied in more advanced cases by small scattered areas of old hemorrhage and hemosiderin pigment, characterize the alterations in this organ

Abdominal pain, either before or during the attack of vomiting, is frequently encountered The pain may be severe and is usually localized in the left upper quadrant although occasionally it may extend to

the right side and be suggestive of acute appendicitis The passage of tarry stools is dependent upon the amount of blood passing through the intestinal tract Headache, weakness, and nausea may likewise be associated with these symptoms

Pallor is usually not noted until after one or more attacks of hemorrhage from the gastro intestinal tract Palpitation and the symptoms of vasomotor collapse likewise accompany hemorrhage, the degree depending on the amount of blood lost

The onset in the second type is insidious, with weakness, fatigue, anorexia, and loss of weight Protuberance of the abdomen may be an early sign Epistaxes and ecchymoses following slight trauma are also early symptoms Melena associated with abdominal cramps occurs late rather than early in the course of the disease Vomiting of blood is seldom observed except in the advanced stages of the disease

Physical examination reveals a significant pallor of the skin and mucous membranes, petechiae or ecchymoses may or may not be present The abdomen is usually prominent and free fluid may be demonstrated in the peritoneal cavity The liver may be palpable but the spleen is constantly enlarged, sometimes extending to the level of the umbilicus

Laboratory Data In the first type, with gastric hemorrhage the initiating symptom, the blood is usually so little altered from normal that it excites no special interest except for the changes resulting from blood loss Immediately after the hematemesis, before blood dilution has occurred, there may be surprisingly little change in the levels of red cells and hemoglobin Within twenty-four to forty-eight hours, however, these levels may be diminished to 2,000,000 per cubic millimeter or less and 40 per cent (6 2 grams) or less, respectively The erythrocytes are normocytic and normochromic with polychromatophilia and reticulocytosis directly proportional in degree to the activity of the bone marrow following the hemorrhage Except for the expected leukocytosis and neutrophilia following hemorrhage, the leukocytes are usually normal in number and in character The platelets are normal in number, the bleeding and clotting times are within normal limits

As the disease progresses a moderate degree of microcytic hypo chromic anemia may develop At such times, also, the number of

varices, the rupture of which accounts for the sudden profuse hemorrhage. The causes for such obstruction may be hepatic disease, portal or splenic thrombophlebitis, pressure on the veins by enlarged lymph nodes, tumors, residual embryonic valves within the veins, or other unusual abnormalities.

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may occur in thrombocytopenic purpura either of the primary type or of the type secondary to leukemia or aplastic anemia The presence of splenomegaly in these conditions may add to the difficulty of differentiation However, changes in the number of blood platelets should identify thrombocytopenic purpura, changes in the numbers and character of the leukocytes and erythrocytes should assist in differentiating primary blood disturbances

Hematemesis resulting from gastric or duodenal ulcers or from a foreign body with trauma to the esophagus or gastric mucosa is not usually associated with splenomegaly The history and the roentgenological examinations offer additional aid in detecting such conditions as the cause of free bleeding

In the form of splenomegaly and anemia with an insidious onset, the diagnosis is often difficult and speculative, it requires, first, the exclusion of other diseases that may produce anemia, leukopenia, thrombocytopenia, and splenomegaly, either singly or in combination Acute or chronic infection must always be excluded in childhood Chronic meningococcemia and tuberculosis of the spleen have been discovered in patients who presented the diagnostic criteria ascribed to splenic anemia Granulomatous infiltrative processes such as visceral sarcoid, as well as lipoid metabolic diseases such as Gaucher s splenomegaly, must likewise be excluded Even chronic passive congestion from long-standing heart failure may produce this picture Leukemia and sclerosing lymphoblastoma should be ruled out by careful examination of the blood, by search for abnormal types of leukocytes, and, if necessary, by examination of biopsy material from a lymph node or bone marrow

Course and Prognosis Hematemesis resulting from the rupture of a thin walled varix in the esophagus or in the stomach may be sufficiently prolonged and severe to cause a fatal termination at any time, either in the first attack or subsequently Such a possibility cannot always be foretold by estimating the amount of blood lost in the vomitus, for a variable amount of blood may pass through the intestinal tract or remain in the small intestine and so make measurements of blood loss impossible Likewise, estimation of the erythrocytes and hemoglobin levels may not be relied upon for evaluating the amount of blood lost, for dilution of the blood does not occur immedi-

leukocytes may be 5,000 per cubic millimeter or less with relative lymphocytosis The platelets likewise may be diminished to low normal levels, thus, the hematologic findings in the first type overlap those usually seen in the second type

Roentgenograms of the esophagus, after ingestion of barium, may disclose esophageal varices

In the second type, which is characterized by an insidious onset, the blood shows constantly a moderate hypochromic anemia The erythrocytes number between 2,000,000 and 3,500,000 per cubic millimeter, and the hemoglobin level is from 40 to 60 per cent of normal The cells are microcytic and hypochromic, and there are relatively fewer polychromatophilic cells or reticulocytes than would be expected according to the severity of the anemia that exists This indicates an inadequate response on the part of the bone marrow

The leukocytes are constantly diminished to 5,000 per cubic millimeter or less, levels as low as 1,500 may be found The polymorphonuclear neutrophils are diminished relatively as well as absolutely, but usually there are no abnormal forms or immature leukocytes The platelets may be lowered to less than 100,000 per cubic millimeter, although occasionally they are at a normal level

The bleeding time may be somewhat increased, to six to eight minutes (normal three to five minutes) The clotting time is normal, and clot retraction is only delayed in the presence of thrombocytopenia The icterus index and the fragility of the erythrocytes in hypotonic saline solutions are normal

Roentgenograms usually show no abnormality other than the presence of fluid in the peritoneal cavity and the enlarged spleen or liver

Diagnosis In patients with sudden and unexpected hematemesis associated with abdominal pain and little or no splenomegaly but subsequent increase in the size of the spleen, the diagnosis of obstruction to the splenic circulation is strongly suggested Additional support may be found in the history of an omphalitis or other infection in early life leading to thrombophlebitis of the portal or splenic vein in later life The demonstration of esophageal varices, either by roentgenogram or by direct examination through an esophagoscope, confirms the diagnosis

Hematemesis as a symptom of a general hemorrhagic tendency

in that extensive thrombosis may lead to a fatal outcome However, the thrombocytes usually fall immediately after an attack of intravascular blood clotting, and the patient may suffer no further similar disturbance

Treatment Operation has become the method of choice in the treatment of both of the types described Splenectomy is indicated as the first step regardless of whether hematemesis or anemia and leukopenia are predominating symptoms, for in both types enlargement and congestion of the spleen are constantly present If in addition there is evidence of interference with the flow of blood through the portal or splenic vein, exploration as to the site of such obstruction is advisable Measures toward the establishment of a collateral circulation are indicated

Patients with the sudden attack of hematemesis should be kept quiet, given sedative such as morphine subcutaneously to relieve anxiety and diminish the tendency to gastric peristalsis, and protected against the ingestion of large amounts of fluid which are craved and may produce further nausea and vomiting

If transfusion with suitable matched citrated whole blood is not immediately available, intravenous fluids or plasma may be used temporarily Transfusion should be repeated at intervals sufficiently frequent to replace to a safe extent the amount of blood lost This must be judged by the condition of the patient and the symptoms exhibited, rather than by measurement of the amount of blood in the vomitus or by estimation of the erythrocyte or hemoglobin levels

After operative interference, particularly splenectomy, the danger of extension of thromboses from the original site is increased both because of the trauma and mechanical manipulation carried out and because of the increase in thrombocytes which invariably follows If the platelets rise to a level of about 1,000,000 or more per cubic millimeter, multiple thromboses are quite likely to occur and may produce severe abdominal pain and high fever, and may even lead to a fatal outcome Such secondary thrombocytosis may be successfully treated by deep roentgen ray exposure or by the intravenous injection of heparin

ately after hemorrhage Only by correct evaluation of the symptoms and clinical signs can fatal collapse from hemorrhage be prevented

The patient may appear entirely well between attacks The frequency and severity of the attacks are dependent upon the site of the obstruction in the portal or splenic system and the efficacy of the collateral circulation which develops Some patients who have been followed through childhood to adult life have had only minor incapacities at the time of the hematemeses and have been in good health between attacks

In general, the establishment of a satisfactory collateral circulation, produced either naturally or as the result of operative assistance, may be judged from diminution or cessation in the attacks of hematemesis and limitation in growth of the spleen, if this organ has not been removed Likewise, extensive dilatation of superficial veins on the trunk suggests the development of collateral circulation which may assist in easing the burden caused by venous congestion If a satisfactory collateral circulation is not or cannot be established, the symptoms increase in severity and a fatal termination may be expected The immediate outcome at the time of hematemesis is dependent upon the speed with which the lost blood is replaced

After puberty, particularly in females, a greater portion of the blood from the obstructed circulation may be carried away through the pelvic vessels, and the patient may suffer from fewer attacks of hematemesis thereafter

The prognosis in the second type of the disease varies with the degree of anemia and splenomegaly Before the days of surgical interference, the course was usually one of slow progression until ascites and hematemesis developed, after which a fatal termination was common With the present mode of surgical intervention, the course has been altered in many instances, so that the patient improves rapidly and has little or no disturbance after operation, the anemia, leukopenia, and thrombocytopenia improving This improvement may last for an indefinite period of time Further experience is needed to determine whether or not the underlying process has been corrected absolutely

Occasionally a rapid rise in thrombocytes follows splenectomy and intravascular thromboses occur Such a complication may be serious

At necropsy, large amounts of blood were found in the stomach and small intestines At least two ruptured varices were demonstrable in the lower end of the esophagus The portal vein and the remains of the splenic vein were filled with an old recanalized thrombus

Comment This case report illustrates the first type of congestive splenomegaly, characterized by the sudden onset of gastric hemorrhages, a varying degree of splenic enlargement related to the episodes of hematemesis, evidences of obstruction to the portal and splenic circulations and the formation of esophageal varices In this child, an early history of infection with gastro intestinal symptoms may have been related to the thrombophlebitis which later manifested itself Splenectomy and omentopexy failed to establish an adequate circulation, and death occurred following another extensive hematemesis At necropsy the almost complete obstruction of the portal circulation was demonstrable

CASE RECORD CONGESTIVE SPLENOMEGALY

(SECOND TYPE BANTI S SYNDROME)

A ten year-old boy was admitted to the hospital because of progressive pallor, loss of weight, and enlargement of the abdomen of one month s duration One week prior to entry he had a severe nosebleed

Physical examination revealed a tall fairly well-developed but thin boy with moderate pallor of the skin and mucous membranes jaundice and petechiae were not present The heart and lungs were normal The abdomen was prominent, the liver was not enlarged but the spleen was easily felt three finger-breadths below the costal margin, a fluid wave was not detectable The genitalia and extremities were normal

The blood showed constantly a microcytic hypochromic anemia with erythrocytes numbering 3,300 000 per cubic millimeter and hemoglobin level of 8 4 grams (54 per cent) The leukocytes were constantly between 3,000 and 5,000 per cubic millimeter reticulocytes were low platelets numbered about 150,000 Differential smears showed no immature or malignant cells The icterus index was not elevated The fragility of the erythrocytes in hypotonic saline solutions was normal Wassermann and tuberculin tests were negative Roentgenograms showed no abnormality other than the enlarged spleen

Splenectomy was performed one month after entry The spleen weighed 307 grams when freed of its contained blood There were numerous fibrous adhesions over the surface The cut section was grayish red with very prominent fibrous tissue and the trabeculae were easily identified The pathologic diagnosis was splenomegaly with extensive fibrosis of the Banti type

Following operation the patient s erythrocyte and hemoglobin levels rose

CASE RECORDS CONGESTIVE SPLENOMEGALY
(FIRST TYPE SPLENO-PORTAL THROMBOSIS)

A six-year-old white female child, vomiting large amounts of blood, was brought to the hospital The past history was important During the first year of life the infant had suffered from erysipelas involving the lower extremities, followed by gastro enteritis associated with high fever, vomiting, and diarrhea for more than two weeks After recovery from this illness her health had been satisfactory

Twenty-four hours before admission, the child complained of severe abdominal pain, headache, and dizziness Eighteen hours before entry she vomited a large amount of fresh as well as clotted blood Six hours before entry there was a repetition of this hematemesis

Physical examination revealed a well developed and well nourished child with marked pallor of the skin and mucous membranes Icterus and petechiae were not present The pulse rate was rapid, and a blowing systolic murmur was heard over the apex of the heart The abdomen was generally tender to palpation but no spasm or masses could be felt The spleen was not enlarged to palpation

The blood showed an erythrocyte level of 2,400,000 per cubic millimeter and hemoglobin of 7 5 grams per hundred cubic centimeters (40 per cent) The platelets numbered 300,000 per cubic millimeter The leukocyte count was 15,000 per cubic millimeter and 85 per cent of these cells were polymorphonuclear neutrophils

Following two transfusions of matched whole blood, the hematemesis ceased and the patient improved rapidly During the following week, the erythrocytes increased to 3,500,000 per cubic millimeter and the leukocytes diminished to 4,500 The spleen gradually became enlarged until it reached to the level of the umbilicus in the mid clavicular line

Roentgenograms, after barium ingestion, revealed the presence of large varices at the lower end of the esophagus and confirmed the tentative diagnosis of obstruction of the circulation through the portal or splenic vein

The site of obstruction or its cause could not be demonstrated by exploratory laparotomy An enlarged spleen was removed, the dilated esophageal varices ligated, and an omentopexy performed to assist in establishing an adequate collateral circulation The spleen, which weighed 300 grams, showed a moderate degree of fibrosis and some hemosiderosis

The child made a satisfactory convalescence and progressed normally until one year after operation At this time she complained again of severe abdominal pain, passed several tarry stools and then vomited a large amount of clotted blood After hospitalization and transfusion, further hematemesis occurred, the blood being increasingly fresh The patient suffered circulatory collapse and died ten hours after admission to the hospital

General Considerations The disease is believed to result from a congenital disorder of the blood forming tissues, the cause of which is still unknown The racial and familial incidence suggests that it is an impure dominant inherited developmental anomaly The earliest hematologic signs—alterations in the size, shape, and hemoglobin content of the erythrocytes—have been found in the fourth week of life

This clinical entity has occurred in twins, in sister and brother, in cousins, and in individuals more distantly related As yet there is no record of parent and offspring both with severe manifestations of this form of anemia, in all probability most such sufferers have succumbed in childhood or in early youth An increasing number of cases, however, are being recognized in which a sibling and one or both parents of children with severe Mediterranean anemia have milder degrees of hypochromic anemia Characteristically, these individuals fail to benefit from iron medication and constantly show irregularly shaped hypochromic erythrocytes

Recently, also, young adults of Mediterranean origin have been found with only moderate degrees of hypochromic anemia resistant to iron therapy, abnormally shaped erythrocytes in the peripheral circulation, some splenomegaly, and widening of the skeletal bones These individuals may have had milder forms of Mediterranean anemia in childhood but were capable of surviving and improving with age

Only children of Mediterranean origin have been afflicted with this unusual disease The rare patient with different heritage said to have comparable changes in the blood has failed to present all the diagnostic criteria for the disease

Symptoms and Signs The usual presenting symptoms are pallor, anorexia, and fatigue, and enlargement of the abdomen due to splenomegaly Periodic attacks of fever accompanied by increasing pallor and jaundice are frequent manifestations The eyes appear slanting and with an epicanthus, the cheek bones are prominent, and protrusion of the teeth added to the yellowish tint of the skin suggests that the patient is of the Mongolian race The heart is frequently enlarged, with hemic murmurs which are easily audible The abdomen becomes increasingly protuberant with progressive

rapidly The leukocytes numbered 58,000 per cubic millimeter on the second day and thereafter gradually fell to a level of about 9,000 On the eighth day post operatively the platelets numbered 800,000 and reached 1,500,000 on the fourteenth day On the twenty-first day, the platelets numbered only 500,000 and were thereafter maintained at this level Two years later the patient was in good health and the blood was being maintained at a normal level

Comment This patient exemplifies the second type of congestive splenomegaly, with an insidious onset of pallor, gradual enlargement of the spleen, and the development of a microcytic hypochromic anemia, leukopenia, and thrombocytopenia Following splenectomy there was rapid improvement which was maintained throughout the period of observation The disease process in this instance may be presumed to have been in the spleen itself, producing the symptom complex known as the Banti syndrome

The ultimate outcome in this type of congestive splenomegaly cannot be predicted with certainty The possibility exists that symptoms of obstruction may develop, and the patient may exhibit hemorrhages from dilated esophageal and gastric varices years after an apparent recovery from the disease

THE ANEMIAS OFTEN ASSOCIATED WITH JAUNDICE

Under this heading are included

a Mediterranean anemia
b Acute hemolytic anemia
c Congenital hemolytic anemia
d Sickle cell anemia
e Erythroblastosis fetalis or hemolytic anemia of the newborn

Mediterranean Anemia

This is a progressive anemia occurring in children from families of Mediterranean origin There is progressive splenomegaly, and large numbers of hypochromic, fragmented, and nucleated erythrocytes appear in the peripheral blood In patients with prolonged severe anemia, a Mongoloid facies and distinctive changes in the bones due to extreme marrow hyperplasia develop

Common synonyms are erythroblastic anemia, Cooley s anemia, thalassemia, myelosis erythroleukemia

The leukocytes also are usually increased in number and tend to be of immature types, such as early myelocytes and young lymphocytes The platelets may be normal or reduced in number

Plates 24 through 29 are illustrative of the blood in this disease

The bleeding and coagulation times are usually within the normal range but occasionally both may be prolonged and epistaxis or post-traumatic hemorrhage becomes serious The serum has an excess of pigment and the Van den Bergh test is indirect The fragility of the erythrocytes in hypotonic saline solutions shows a wider resistance span than normal

The urine and the feces frequently show increased amounts of urobilinogen

Roentgenograms reveal constant changes in the bones, varying in degree in different patients and in different bones of the same patient and with a tendency to become more marked as the disease progresses The medullary trabeculations are unusually prominent, especially in the diaphyses of the long bones and in the ribs This is detected earliest in the small bones of the hands and feet The cortex becomes thin, and circumscribed areas of decreased density are seen occasionally *in the cancellous bone There is apparent thickening of the* flat bones, most striking in the skull There is thinning of the tables with increased porosity, and often it is impossible to identify the outer table as a distinct plane The medullary portion is greatly thickened in the early stages it presents a mottled, spongy appearance, whereas in the late stages there are prominent vertical striations

Diagnosis The familial and racial incidence, the peculiar facies and skin discoloration, the pallor, the splenomegaly, and the characteristics of the blood substantiate the diagnosis *An important feature seen in this type of anemia is the large number of macrocytic hypochromic erythrocytes* Infection and dietary disturbance producing iron deficiency anemia in a Greek or Italian child may simulate some of these changes The roentgenograms of the bones are important in identification Congenital hemolytic anemia and sickle cell anemia may produce similar though less marked changes in the bones but the characteristic blood findings should serve to distinguish these diseases The number of nucleated cells found in the peripheral blood and their immaturity occasionally are suggestive of leukemia, how-

splenomegaly and hepatomegaly The lymph nodes are only slightly enlarged The skin is pale and yellowish brown, and the eyes show mild icterus in the sclerae Ecchymoses and free bleeding may occur in the advanced stages of the disease Retardation in growth and development becomes extreme, especially when the anemia appears in early infancy

Secondary to this profound disturbance in the entire hematopoietic system are the diffuse deposits in the skin and viscera of both iron containing and iron-free pigments associated with blood formation The extensive extramedullary hematopoiesis is widespread throughout the body but most marked in the spleen and the lymph nodes The severe hyperplasia of the marrow in the long and flat bones and the skull, which is responsible for the increase in the width and thickness of these structures, compresses the trabecular bone Because of the resulting thinness of the cortical bone, pathologic fractures are not uncommon

Laboratory Data The average number of erythrocytes is about 3,000,000 per cubic millimeter, although in severe cases the level may fall to less than 2,000,000 The hemoglobin content is usually far lower than the cell level, giving a color index 0 5 or less The peculiarity so apparent in the stained blood film is the extreme variation in both size and shape of the cells associated with a high degree of hypochromia Macrocytes of 15 micra diameter and microcytes of 3 micra are common Tailed erythrocytes and fragments of cells are numerous Polychromatophilia, basophilic stippling, Howell-Jolly bodies, Cabot rings, and reticulated cells appear frequently Above all, nucleated red cells in numbers and of types seen in few other diseases abound in every field Erythrocytes in every stage of development may be seen Multi-nucleated cells appear occasionally Macrocytes with unusual central and peripheral deposits of hemoglobin—therefore named target cells —are often seen Irregularity of hemoglobin deposit in the cells and evidence of fragmentation may be the earliest signs of the disturbance After removal of the spleen, a striking feature is the tremendous increase in the number of nucleated erythrocytes in the peripheral circulation, the level remains constantly elevated thereafter to as high as 300,000 to 400,000 per cubic millimeter

and slight jaundice of the skin and sclerae The abdomen had become prominent, the patient had failed to gain in weight, physical activity had diminished, and difficulty in breathing after slight exertion was noted

Physical examination revealed an under nourished and under developed child The distinctive features by inspection were short stature, extreme pallor, a prominent abdomen, and Mongoloid facies suggested by the prominence of the forehead and the malar bones, an epicanthal fold of the eyelids, and a yellowish tint to the skin The sclerae, as well as the skin, showed slight icterus The heart was enlarged, and there was a loud blowing systolic murmur heard all over the precordium The liver extended 3 centimeters below the costal margin, and the spleen was felt as a firm, sharply notched organ reaching the mid line at a level 2 centimeters below the umbilicus Pulse and respirations were rapid

The erythrocytes numbered 2,500,000 per cubic millimeter and the hemoglobin level was 4 7 grams per hundred cubic centimeters of blood or 30 per cent The nucleated cells numbered 35 000 per cubic millimeter, of which 22,000 were nucleated erythrocytes giving a corrected leukocyte level of 13,000 per cubic millimeter In the stained blood smears there was extreme variation in size and shape of the erythrocytes with diffuse basophilia and occasional stippled cells All varieties of nucleated erythrocytes were visible though the majority were erythroblasts The most striking feature was the variation in size of the erythrocytes which, although predominantly microcytic hypochromic cells also showed many macrocytes markedly deficient in hemoglobin and having a peculiar distribution of hemoglobin in the center of the cell There were many immature myelocytic forms of leukocytes the platelets appeared only slightly diminished

Roentgenograms showed widening of the medullary portion of the skull and of the long bones with thinning of the cortices There was generalized osteoporosis with accentuated trabeculation The heart was enlarged, and the liver and spleen likewise were increased in size

During his fifth year the child was treated for the symptoms of pneumonia at another hospital, and after recovery from this acute illness, splenectomy was performed there There was no improvement in his anemia following this operation but the nucleated erythrocytes in the peripheral blood increased from a level of about 10,000 per cubic millimeter to over 200 000 per cubic millimeter and remained between 200,000 and 350,000 thereafter

During the ensuing eight years the patient has had frequent recurrences of feverishness accompanied by increasing pallor and jaundice The peculiarities of the blood have been constantly maintained and the extreme variation in size and shape of erythrocytes has become somewhat accentuated Transfusion has been given on several occasions when the erythrocyte level has fallen markedly and the patient has developed signs of cardiac decompensation from profound anemia The liver has increased in size so

ever, the striking abnormality of the erythrocytes rather than of the leukocytes, and the number of nucleated erythrocytes as well as the changes in the skull and the long bones, should help to dispel any doubts as to diagnosis

Course and Prognosis Most of the children with moderate to severe forms of the disease have succumbed from profound anemia or intercurrent infection within a few years after the earliest appearance of symptoms However, there are rare instances in which patients are living and leading fairly active lives after a duration of a dozen years Therefore the course cannot be accurately predicted In general it may be said that the more profound the anemia and the earlier its onset, the more rapidly the disease progresses to a fatal result Recent reports in the literature indicate that adults with mild forms of this anemia are not uncommon

Treatment Since there is no specific form of therapy the treatment should be directed toward the relief of symptoms and the prevention of complications Transfusion is frequently necessary in the younger, more anemic infants to prevent anoxemia, cardiac dilation, secondary pneumonia, and death Iron, liver, or liver extract, both orally and intramuscularly, have been used without producing lasting benefit The removal of the spleen is contraindicated as this procedure has not been followed by retardation in the progress of the disease, the hematological changes continue unabated, the number of nucleated erythrocytes in the circulation increases, and the anemia may progress even more rapidly

Exposure to deep roentgen-ray therapy over the spleen and the long bones is of questionable value and at best is followed by only transient effect

CASE RECORD MEDITERRANEAN ANEMIA

A three-and a half year-old Italian infant was brought to the hospital because of increasing pallor and prominence of the abdomen The parents, who were distant blood relatives, had been born in Sicily The mother had had three previous pregnancies Two children were alive and entirely well, but one child had died of anemia at two years of age

The infant seemed normal at the time of birth At one year of age he appeared slightly pale and his appetite diminished In the following two years there had been frequent bouts of feverishness with subsequent pallor

sionally fatigued During the previous two years there had been mild bouts of fever lasting one to two days followed by an increase in the yellowish color of the eyes and the abdomen had become prominent

Physical examination showed a well developed and well nourished boy with slight pallor of the lips and mucous membranes and a slight but definite icteric tint to the sclerae and skin There was no suggestion of Mongoloid facies The heart was not enlarged but a loud systolic murmur was audible over the apex The abdomen was somewhat prominent The liver was palpable two finger breadths below the costal margin, and the spleen was palpable at the level of the umbilicus in the mid clavicular line

The erythrocyte count was 4 750,000, the hemoglobin 7 grams per hundred cubic centimeters of blood (41 per cent) the leukocytes numbered 7,350 and the platelets 300,000 per cubic millimeter Stained blood smears showed normal appearing leukocytes, and marked variation in the size and shape of the erythrocytes with predominantly microcytic hypochromic cells but also many macrocytic hypochromic cells containing irregular deposits of hemoglobin There were five nucleated erythrocytes per hundred nucleated cells The icterus index was 20, the fragility of the erythrocytes in hypotonic saline solutions showed a slight increase in resistance span

Roentgenograms revealed slightly increased porosity of all the skeletal bones with only minimal increase in thickness of the skull bones All these changes were much less marked than is usual in patients with Mediterranean anemia

During the following four years the patient continued in a fair state of health with relatively little change in his physical signs or in his blood levels The administration of liver and especially of iron in large amounts in an effort to correct his lowered hemoglobin concentration produced no change Recurrent respiratory infection and attacks of measles and of pertussis likewise produced no alterations in the child s general condition and only slight leukocytosis and a slight increase in the number of nucleated erythrocytes in the peripheral blood He has been able to attend school and remains in relatively good health, except for the constant mild icterus and anemia His activity is moderately limited

Comment This case represents a Mediterranean anemia of mild degree with the onset of symptoms recognizable by the parents relatively late in childhood There was only a slight degree of jaundice and anemia during crises of hemolysis, the spleen and the liver were only moderately enlarged, the erythrocyte level was not greatly diminished and the hemoglobin concentration was about half the normal value There were typical macrocytic hypochromic cells, very much flattened in appearance, in the peripheral blood and these had irregular deposits of hemoglobin of the type sometimes

it reaches almost to the pelvic brim The widening of the marrow spaces in the skull and the long bones has continued due to increased hematopoietic tissue The cortical bone has become increasingly thin, and pathologic fractures have occurred on many occasions from slight trauma or from strain to the radius, the tibia, and the fibula The patient continues to lead a moderately restricted life with diminished activity and frequent bed rest, and his growth and development at the age of eleven years is that of a child of seven Therapy directed toward improvement in his blood state has been ineffective except for transfusion administered when anemia became severe and dyspnea was apparent

Comment This exemplifies a case of Mediterranean anemia of great severity The family history in such instances often reveals one or more siblings suffering from or dead from this anemia The age of onset was early in infancy and this forebodes a rapid progress in the disease and consequently profound anemia Severe pallor and enlargement of the spleen and liver were noted after the frequent attacks of feverishness with hemolysis The increasing hypertrophy of red marrow substance in the skeletal bones produced changes in the skull and facies easily recognizable by inspection as well as thinning of the long bones which resulted in pathologic fractures The erythrocytes were constantly lowered in number, and the hemoglobin level was even more profoundly diminished The number of nucleated erythrocytes in the peripheral blood varied from 5,000 to 30,000 per cubic millimeter, and after splenectomy was performed there was a rapid increase in the number of these cells to several hundred thousand per cubic millimeter with no evidence of improvement in the blood or in the general health of the patient

In the majority of instances transfusion has been necessary after many of the hemolytic crises since the hemoglobin level may fall to 4 grams or less and symptoms of cardiac decompensation may develop Most of the patients so far reported with such severe type of Mediterranean anemia have succumbed either to anemia or to intercurrent infection during infancy or childhood Only in rare instances, such as this case illustrates, has there been a continuation of the process for ten years or more and, even so, limitation of activity and delay in growth and development have been marked

CASE RECORD MEDITERRANEAN ANEMIA

A seven year-old boy was brought to the hospital because of jaundice and a prominent abdomen, a condition of two years duration The parents had been born in Italy, and were in good health One other child was living and had no symptoms similar to the patient s

His health had been good until two years before entry, at which time it was noted that the sclerae were becoming yellowish and the child was occa

patients with acquired hemolytic anemia Widal emphasized the phenomenon of auto agglutination in such cases and various types of hemolysins were demonstrated in the serum of patients with the disease Since 1930, such lytic substances have been studied and isolated by numerous observers Recently more detailed observations have been made by Dameshek and the literature has been comprehensively reviewed by him

The disease may occur at any age after the first year of life it affects both sexes and all races without distinction

The relationship to acute or chronic infection has not been precisely defined In a large proportion of cases, infection has been present shortly before the onset of symptoms of hemolytic anemia, usually with an interval of from one to two weeks between the time the infection subsided and evidences of hemolysis appeared This suggests a sensitization phenomenon

Although the majority of cases of acquired hemolytic anemia are acute in type and after recovery show no tendency to relapse, a few instances have been recorded in which the disease becomes subacute or chronic and may even recur after apparent recovery

Symptoms and Signs A sudden onset is typical Nausea and vomiting may be noted as the first signs of illness These are rapidly followed by malaise, restlessness, and irritability Fever and lethargy are also prominent symptoms Generalized abdominal pain, weakness, dyspnea, and palpitation of the heart are common complaints during the first days of illness

The passage of bright red or port wine colored urine—hemoglobinuria—may be the earliest evidence of destruction of blood If this sign is absent or after it subsides, the urine may appear orange colored and the feces likewise have an orange tint, due to the presence of large amounts of urobilinogen in the excreta Visible jaundice of the skin and the sclerae and profound pallor rapidly follow these earliest evidences of blood destruction

Physical examination at the time of onset reveals pallor, slight to moderate icterus, high fever, dyspnea, and tachycardia in a sick looking patient The heart may be enlarged and hemic murmurs may be easily audible The liver is frequently enlarged, the spleen is constantly increased in size as well as occasionally tender to palpation

labeled "target cells." The number of nucleated erythrocytes in the peripheral blood was low. The hyperactivity of the marrow in the long bones and in the skull was not sufficiently great to produce the marked changes in these skeletal structures usually seen in the more advanced cases of Mediterranean anemia. Likewise, none of the physical stigmata seen in the facies of patients with the severe type of disease was present here. Since the physical changes as well as the appearance of the bones in roentgenograms are dependent on the amount of hyperplastic marrow tissue causing pressure atrophy on growing bones, it is reasonable to expect that there will be less of this type of change in a patient with Mediterranean anemia of only moderate severity. In this connection, it should also be kept in mind that even in the most severely affected patients, the characteristic changes in the long bones are not demonstrable early in infancy since they have not had sufficient time to develop before the age of at least one year.

As in this case, the patient's general health may remain good except for the attacks of feverishness associated with hemolysis. The administration of iron, liver, or any other stimulant to hemoglobin formation is of little benefit. However, since the hemoglobin value in this case was not sufficiently diminished to produce marked symptoms of anemia, transfusion was not indicated. On the basis of accumulating experience with the milder forms of this congenital disturbance in hematopoiesis, there is reason to hope that these patients may continue well and may even improve with age.

Acute Hemolytic Anemia

The acute form of acquired hemolytic anemia is characterized by the sudden onset of blood destruction, as evidenced by jaundice, anemia, and often hemoglobinuria.*

General Considerations. The original descriptions of this form of anemia are often overlooked. In 1907, Chauffard described it as an entity distinct from the familial form of hemolytic anemia. At about the same time Widal and his collaborators, and in 1908 Hayem, likewise described the acute acquired form of hemolytic anemia. Attention was redirected to this disease by Lederer in 1925, and thereafter his name was occasionally attached to it.

In the original descriptions of Chauffard and his co-workers, it was pointed out that an iso-hemolysin was present in the serum of

* This disease may be caused by toxins and drugs and will be seen with greater frequency as the use of sulfonamide therapy increases. This specific etiologic agent must therefore be excluded in differential diagnosis.

pears quickly and does not reappear after the second day of illness Large amounts of urobilinogen in the urine and in the feces frequently give the excreta a dark-colored, somewhat orange tint By actual measurement urobilinogen or urobilin may be present in concentrations ten or more times the normal Bile is not found in the urine but is present in normal amounts in the feces

Diagnosis The sudden development of hemoglobinuria, icterus, and anemia in a child who has previously suffered from an acute infection even of mild degree, the symptoms of sudden blood want, the enlargement of the spleen, and the typical changes in the blood are suggestive of acute hemolytic anemia If hemoglobinuria is absent and the erythrocytes are not predominantly macrocytic, it may be difficult to differentiate between acute hemolytic anemia and the first attack of congenital hemolytic anemia, for the latter form does not always have a clearly established hereditary basis Only further observation of such patients may clarify the diagnosis

Sepsis, particularly of the streptococcal type, may produce a hemolytic state, but in such instances the evidences of severe infection usually overshadow those of the hemolytic process

Acute leukemia, when associated with rapid development of anemia, splenomegaly, and leukocytosis, may be difficult to differentiate from acute hemolytic jaundice However, the presence of a hemorrhagic tendency with a diminution in platelets, the absence of any notable features of increased blood destruction, and the high percentage of blast forms of white blood cells are indicative of leukemia

Course and Prognosis The course is usually acute and of short duration Commonly after a single transfusion or, occasionally, a small number of transfusions, the hemolytic tendency disappears and the patient recovers Occasionally the disease becomes more prolonged into a subacute or chronic form which improves only slightly or fails to improve following transfusions

The prognosis is usually good After one to two weeks the evidences of hemolysis gradually diminish and the patient s erythrocyte and hemoglobin levels improve rapidly Complete recovery may take place within a month of the onset of the disease

If, when the symptoms first appear, the anemia progresses rapidly and the patient exhibits signs of acute blood loss, delay in transfusion

Laboratory Data. The erythrocyte level at the onset varies tremendously. Although in the milder cases there may be as many as 4,000,000 red blood cells per cubic millimeter, more commonly a profound anemia is present and a level of 1,000,000 or less is found. The hemoglobin concentration is proportionately low, although occasionally a greater concentration of hemoglobin in comparison with the erythrocyte level yields a color index greater than one. Stained films of the blood are notable for the presence of large numbers of macrocytic cells well filled with hemoglobin. Polychromatophilia is a notable feature and when blood films are stained with brilliant cresyl blue a high percentage of reticulocytes is seen. It may be noted that the reticulated erythrocytes are principally cells of large size. Occasionally, in the most acute cases, there may be evidences of destruction of erythrocytes in the stained smear as judged by fragmentation of these cells.

In the rare cases mentioned previously when the disease becomes chronic, the macrocytic cells may diminish and typical microcytic spherical erythrocytes may appear in increased numbers in the peripheral blood, presenting a blood picture commonly associated with the chronic congenital form of hemolytic anemia.

The number of leukocytes is constantly elevated, often to an extreme degree. In some instances more than 50,000 white cells per cubic millimeter have been found. A high percentage of the leukocytes are polymorphonuclear neutrophils and immature forms of the myeloid series. The granulation in the cytoplasm of the neutrophils may be of the "toxic" variety.

The platelet level is frequently elevated above 400,000 per cubic millimeter, and the bleeding and clotting times are normal.

Plate 30 shows the blood cells in acute hemolytic anemia.

The fragility of the erythrocytes in hypotonic saline solutions varies considerably. Occasionally there is no evidence of increased hemolysis by this test, but in many instances hemolysis may begin in 0.5 per cent of saline solution or even in almost isotonic saline solution so that this test may yield a result similar to that found in the congenital form of the disease.

Frequently at the onset there is gross hemoglobinuria, producing a red or port-wine colored urine. Usually, this abnormality disap-

cussion and a loud blowing systolic murmur was heard over the left chest The abdomen seemed full, and palpation showed enlargement of the spleen down to the level of the umbilicus and of the liver two finger-breadths below the costal margin

The erythrocytes numbered 2,200,000 per cubic millimeter, the hemo globin level was 7 8 grams or 50 per cent the leukocytes numbered 35 000, and the platelets 350,000 Stained smears of the blood showed a reticulocyte level of 35 per cent and erythrocytes of the normocytic normochromic type with occasional macrocytes well filled with hemoglobin The leukocytes were predominantly polymorphonuclear cells, many of which had toxic granulation in the cytoplasm

The urine was clear, port wine in color gave a positive test for albumen, and on microscopic examination showed much cellular debris but no erythrocytes The guiac test was strongly positive The icterus index was 30, and the fragility test showed no change from normal values

Immediately after entry the patient was transfused with 200 cubic centi meters of matched citrated whole blood The pulse fell in rate from 150 per minute to 110 per minute, and the respirations from 40 to 28 per minute However, the urine continued to be grossly bloody looking and by the next morning the patient was more deeply jaundiced and the pulse and respirations had once more increased in rate The erythrocyte level at this time was 1 400,000 per cubic millimeter He was therefore again transfused with a similar amount of blood with only transitory improvement Evi dences of hemolysis continued and on the third day after entry the erythrocyte count was 960,000 per cubic millimeter Two larger transfusions were given at this time The following day the number of red cells had increased to 2,500,000 per cubic millimeter and the urine began to show less hemo globin and less urobilinogen

During this time the temperature had fluctuated between 101°and 104°F On the fifth day there was a fall in temperature to 99° and thereafter no elevation beyond 99 6°F The pulse and respirations likewise diminished to normal levels

The erythrocytes increased steadily in number until the ninth day after entry when an erythrocyte count showed 3,100 000 per cubic millimeter and hemoglobin of 8 4 grams or 54 per cent The leukocytes numbered only 12,000 per cubic millimeter The reticulocytes were 9 per cent and the number of polymorphonuclear neutrophils with toxic granules had dimin ished to 2 per cent In the stained smears at discharge, the erythrocytes appeared normal in size and hemoglobin content

Comment Acute hemolytic anemia may develop in a child so suddenly that the symptoms of blood want appear early As in this patient a previ ous pharyngitis or respiratory infection is often noted Hemoglobinuria occurs more frequently with this type of hemolytic anemia than with any

may endanger life, and a guarded prognosis must be given until the severity of the hemolytic process abates Also, in the rare form of recurrent or chronic hemolytic anemia of the acquired type, crises of severe hemolysis are cause for concern and here again the prognosis should be guarded

Treatment Transfusion is the most satisfactory method for the treatment of acute hemolytic anemia The injection into the circulation of unaltered erythrocytes prevents the development of symptoms of serious blood want In addition, the blood plasma may protect against the further hemolytic tendency and produce a cessation of blood destruction in the patient It is important to administer fresh rather than stored blood, compatibility of the infused blood for the Rh factor as well as for other factors should be determined as often as transfusion is given throughout the course of the disease

It has recently been emphasized that in the recurrent or chronic type of acquired hemolytic jaundice, splenectomy may become imperative if transfusion alone, even repeated often, fails to produce a permanent remission In such instances, this operative procedure may be followed by results equally as satisfactory as those obtained in congenital hemolytic anemia

CASE RECORD ACUTE HEMOLYTIC ANEMIA

A two-year old boy was referred to the hospital because of rapidly developing pallor and jaundice of four days duration The family history and past history were not contributory

Ten days before entry he suffered from a moderately severe acute pharyngitis with high fever and pain in the throat for three days This subsided rapidly and the child felt entirely well Four days before entry an increasing lassitude and sleepiness were noted The appetite became poor and the patient appeared pale Two days before entry the pallor was more noticeable and the child complained of constant fatigue Twelve hours before entry jaundice of the skin and of the sclerae was apparent At about this time the child voided a small quantity of bright red urine, he continued to pass bloody urine in increasing amounts up to the time of admission

Physical examination disclosed a small but well nourished, alert child with moderate apprehensiveness of his surroundings and rapid respirations and pulse There was slight icterus of the skin and of the sclerae and pallor of the mucous membranes The heart was slightly enlarged to per-

It is reported that the highest incidence of congenital hemolytic anemia occurs among people of Germanic origin However, no racial preponderance has been found in this country, and no greater incidence in one sex than the other

Symptoms and Signs The disease is characterized by crises of hemolysis Between such attacks there may be a mild degree of icterus and a slight anemia At the time of the crisis the jaundice becomes more intense and the anemia rapidly more severe, and the patient may complain of weakness, palpitation, and abdominal pain, especially in the region of the spleen Unexplained fever may usher in the crisis and persist throughout the period of active blood destruction Physical examination reveals, in addition to icterus and pallor, splenomegaly, sometimes hepatomegaly, increased pulse rate, an enlarged heart, and hemic murmurs With recurrent attacks of jaundice and anemia, the nutritional state of the child is affected There is retardation in growth and in the development of the skeletal system, especially delayed ossification of the bones After many attacks of hemolysis with continued hyperbilirubinemia, gallstones may form, even in a young child, and by passage into the common duct may produce symptoms of biliary obstruction

Increased hematopoietic activity in the bone marrow and in the spleen and lymph nodes and moderate enlargement of the heart are dependent upon the degree of the anemia and are not pathognomonic of the disease The moderately large spleen usually exhibits little fibrosis, only slight to moderate hemosiderosis, some depletion of the white pulp, and moderate dilatation of the sinuses, which are lined by an endothelium more prominent than normal

Laboratory Data Although the number of erythrocytes and the level of hemoglobin may be normal during remissions from hemolysis, they tend to fall rapidly during a hemolytic crisis In a few instances a count of less than 1,000,000 red cells per cubic millimeter and less than 3 grams of hemoglobin per cent have been found The color index is usually about unity The red cells, often referred to as spherocytes, are typically smaller and thicker than normal Reticulocytes are constantly more numerous and at the time of a hemolytic crisis may number between 25 and 75 per cent of the total number of erythrocytes

other disease in childhood A single transfusion sometimes suffices to halt the further destruction of blood but more often several transfusions are necessary before this result is attained As in this child, it may be necessary to give transfusions very often in the first few days in order to maintain a satisfactory level of red blood cells Usually when the evidences of hemolysis disappear the patient begins to improve rapidly

In the blood of this child, at entry, there were large numbers of reticulocytes and of macrocytes The fragility of the erythrocytes in hypotonic saline solutions was normal Such findings are usual in acute hemolytic anemia in contrast to the microcytic globular erythrocytes and the increased fragility of the blood in patients with congenital hemolytic anemia

Congenital Hemolytic Anemia

This congenital and often familial disease is usually associated with an increased production as well as an increased destruction of erythrocytes The red cells are predominantly microcytic and globular (spherocytes), excessively fragile, and tend to undergo hemolysis suddenly leading to crises, during which jaundice, anemia, and splenomegaly increase Synonymous terms for this disease are chronic hereditary hemolytic jaundice, familial acholuric jaundice, hemolytic ictero-anemia, and Minkowski-Chauffard disease

General Considerations It is generally thought that the disease is an expression of a dominant hereditary defect in the hematopoietic system which leads to the production of the more fragile globular microcytes Some observers assume the presence of a lytic agent in the blood serum as the causative factor It has also been suggested that increased destruction of erythrocytes in the spleen may play a primary role The inherited defect, however, may be present in so mild a form as to escape ordinary clinical observation

The tendency to hemolysis may exist for months or years in a latent state before some precipitating cause produces a crisis The usual age of onset, therefore, is said to be the second decade of life Although severe crises of hemolysis with prolonged anemia have been seen in patients less than a year old, infants are relatively free of this disturbance When the disease appears in infancy it is of a more severe form, there is a greater degree of jaundice, a more intense anemia, and the crises recur at more frequent intervals

Course and Prognosis The disease is more severe in infants and children than in adults, a chronic low-grade form with only a slight degree of anemia is rarely seen Unlike the usual adult patient who is more jaundiced than sick, the child is much more sick than jaundiced Recurrent crises of hemolysis may produce so severe an anemia as to endanger life Repeated and frequent episodes of hemolysis, which are more common because of recurrent acute infection to which children are more susceptible, often interfere with growth and nutrition Specific therapy is therefore indicated as early as the diagnosis has been accurately established Following splenectomy, either a complete remission from the hemolysis and anemia takes place or a much milder state of the disease results, permitting rapid improvement in growth, nutrition, and activity *

Treatment In childhood, for the reasons mentioned above, splenectomy is the treatment of choice (see Chart 16) The result is most satisfactory except when post-operative platelet crises and thromboses occur (see Chart 19, page 141) The secondary effects from chronic and severe anemia are relieved by early operation Medicinal therapy as a curative measure, such as the use of liver and liver extract, even parenterally, has not been of permanent benefit Deep x ray therapy over the spleen has not produced lasting relief Transfusion is of benefit for temporary amelioration of the symptoms and as a necessary pre operative precaution Medicinal iron may be of benefit for the rapid restoration of the hemoglobin level after a crisis of hemolysis as well as after operation

CASE RECORD CONGENITAL HEMOLYTIC ANEMIA

A four and-one half month-old female infant was brought to the hospital with an anemia of two months duration

The family history showed no other instances of anemia or jaundice Three siblings were living and well Examination of their blood as well as of the parents, offered no suggestion of a blood dyscrasia similar to the patient s

Immediately after birth the patient had been attended by a competent

* Of more than forty operated cases only two patients failed to show improvement In both instances excessive hemolysis continued and the cases terminated fatally No accessory splenic tissue was present to account for the failure in either case

The erythrocytes are excessively fragile when tested in hypotonic saline solutions *Hemolysis usually begins in 0 50 to 0 85* per cent of saline instead of the normal level of 0 45 per cent, and is complete in 0 40 to 0 50 per cent instead of the normal 0 30 to 0 35 per cent The increased fragility of the red cells may persist and the typical cells may maintain their globular shape even after the spleen has been removed The platelets are often increased and the bleeding and coagulation times are normal or decreased during crises of hemolysis The blood serum contains an increased amount of bilirubin as measured by the icterus index or the Van den Bergh test

The leukocytes are usually elevated during periods of hemolytic activity and immature types of myeloid cells are then common Between attacks, these disappear

Plates 31 and 32 show blood cells in congenital hemolytic anemia

The urine and the feces contain large amounts of urobilinogen which imparts to the excreta an orange color Rarely, transitory hemoglobinuria may appear at the onset of a severe crisis

Roentgenograms of the skull and of the long bones often reveal widening of the marrow spaces and thinning and increased radiability of the bones These changes are indicative of hyperplastic bone marrow associated with chronic anemia in childhood In this disease they serve to confirm the presence of a constantly hyperactive, red bone marrow

Diagnosis The clinical and laboratory criteria for diagnosis are distinctive a known family history, and anemia with globular-shaped erythrocytes, splenomegaly, hemolytic crises, increased reticulocytes, and fragility of the erythrocytes Confusion arises from the presence of acute or chronic infection during a first attack of jaundice and anemia In such instances an acquired hemolytic jaundice induced by the infection, rather than the congenital form, may be present and only a further period of observation can clarify this question Sickle cell anemia in the Negro and Mediterranean anemia in the Italian or Greek child may give symptoms similar to those of congenital hemolytic anemia, but the characteristics of the blood cells should serve in differentiation In the neonatal period erythroblastosis fetalis and congenital anemia of the newborn, as well as acute pyogenic infection and syphilis, must be excluded

was distended The spleen filled the left flank to the level of the crest of the ilium and extended to the midline as far as the umbilicus The liver was enlarged about 4 centimeters below the costal margin

At the time of admission the erythrocytes numbered 1,500 000 per cubic millimeter, hemoglobin was 24 per cent, an uncorrected white blood count showed 45,000 cells per cubic millimeter, in the stained smears there were 40 nucleated erythrocytes per 100 nucleated cells, as well as 31 per cent reticulocytes Many of the leukocytes were immature The fragility of the erythrocytes in hypotonic saline solutions showed hemolysis beginning at 0 85 and complete at 0 38 per cent (control 0 46 to 0 30 per cent) The Van den Bergh test was indirect and showed four times normal bilirubin content In the urine and the feces there were excessive amounts of uro bilinogen Roentgenograms showed only a moderate enlargement of the heart

During the first week of observation, the temperature was only occasionally elevated above 100° F There were no detectable evidences of acute or chronic infection or of toxemia Transfusion with matched citrated whole blood was given on two successive days and then laparotomy was performed At operation a large, firm, rough surfaced spleen weighing 44 grams was re moved Further observation showed an enlarged but normal appearing liver Following operation a rapid improvement in blood levels occurred Five days post-operatively the erythrocytes numbered 2 300,000 per cubic millimeter and the hemoglobin was 36 per cent eight days later the counts were 4,000,000 cells and 59 per cent The icterus of the skin and sclerae and the bilirubinemia rapidly subsided The infant was discharged twelve days after operation, in excellent condition

During the ensuing three years the blood levels remained within normal limits, the patient gained and grew in normal fashion and had no further attacks of jaundice or pallor The excessive fragility of the erythrocytes slowly decreased although at the last examination the values were still somewhat above normal Roentgenograms showed relative decrease in the size of the heart in comparison with the chest, while by auscultation the cardiac murmur had disappeared

Comment The first symptoms of hemolytic anemia appeared in this infant at the early age of two and one half months The rapidity of the development of the anemia and its severity are characteristic of the prog ress of this disease when it is first observed in infancy As seen in this case, pallor was more noticeable than jaundice, the heart became enlarged quickly, and audible murmurs developed The spleen and the liver were enlarged far beyond the average size usually seen in older patients The tentative diagnosis of congenital hemolytic anemia was readily confirmed in this patient by the increased fragility of the red blood cells, the reticulocy

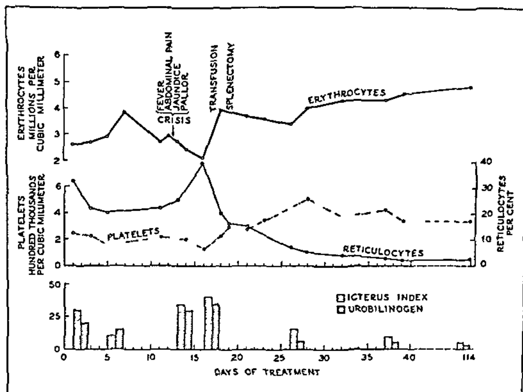


CHART 16 Congenital hemolytic anemia, typical course in a child This was a case of moderate severity in a six year-old patient Note the fall in erythrocytes and the increase in reticulocytes at the time of the hemolytic crisis Following splenectomy there was rapid improvement with disappearance of most of the diagnostic criteria for the disease

physician under whose care she had remained Neither jaundice nor pallor had been observed

The present illness began at the age of two and one half months when the parents noticed a definite pallor which gradually increased in severity during the next two weeks At the age of four months, two weeks before entry, this pallor was very marked An examination of the blood at this time showed an erythrocyte count of 2,000,000 per cubic millimeter and hemoglobin of 40 per cent In the stained smears of the blood there appeared to be many nucleated erythrocytes There was an increase in pallor during the two weeks before entry and a slight degree of jaundice became apparent There was also occasional transitory feverishness

The physical examination revealed a well developed and well-nourished infant weighing twelve pounds She was bright and alert There was marked pallor of the skin and mucous membranes and slight icterus of the skin and sclerae The heart was enlarged to percussion and a loud blowing systolic murmur could be heard over the entire precordium The abdomen

to radiate to the shoulder The patient suffered with this repeatedly An episode of severe pain was accompanied by clay colored stools and bile in the urine and jaundice of increased intensity Roentgenograms at this time showed many small opaque bodies in the right upper quadrant characteristic of gallstones

Six months later, at the age of eleven and one half years an acute hemolytic crisis of unusual severity was followed by extreme dyspnea with signs of diffuse pneumonia, according to the physician who attended the patient at home Two days after the onset of this illness the patient died Autopsy was not obtained

Comment In this family hemolytic anemia appeared in members of three generations and the disease manifested itself in a severe form in the child In him, in contrast to his adult relatives, the hemolytic crises were more frequent and more severe and there was no apparent tendency to outgrow the disturbance As the result of the chronic anemia the heart became enlarged, and there was retardation in bone growth The relatively infrequent childhood complication of cholelithiasis likewise appeared with a subsequent attack of obstructive jaundice Finally, following an acute hemolytic crisis of unusual severity, signs of pneumonia, possibly due to cardiac decompensation and anemia, developed as the terminal event a complication which is constantly to be feared when proper treatment is not instituted promptly after the diagnosis has been established

Sickle Cell Anemia

This is an hereditary and congenital disease of the hematopoietic system occurring almost entirely in members of the Negro race It is characterized by the presence of crescent shaped or sickle-shaped red blood cells which under certain conditions are hemolyzed in excessive numbers, resulting in anemia Synonyms for the condition are sicklemia, meniscocytosis, and drepanocythemia

General Considerations Although rare instances have been reported as occurring in persons of undoubted purely white heritage, the disease is practically limited to the Negro race It has been observed in all parts of the world Females are affected more often than males From numerous investigations, it appears that between 5 and 10 per cent of all Negroes possess the sickling trait, but less than 10 per cent of individuals showing sicklemia develop an associated anemia Although the young are more prone to the disease than the elderly, it may occur at almost any age, even in the neonatal period

tosis, and the evidences of increased hemolysis both in the blood and in the urine and feces As sometimes happens in infancy nucleated erythrocytes were unusually numerous in the peripheral circulation

Operation resulted in a prompt and satisfactory improvement During the period of observation extending over several years there was no recurrence of the hemolytic crises and growth and development were normal This represents the satisfactory results of early diagnosis and prompt surgical treatment of the young infant with congenital hemolytic anemia

CASE RECORD CONGENITAL HEMOLYTIC ANEMIA

An eight-year-old boy was referred to the hospital because of periodically recurring episodes of feverishness followed by jaundice and pallor, from the first year of life The mother, a maternal uncle, and the maternal grandfather had had mild attacks of jaundice and pallor throughout life, but never of sufficient severity to require medical attention, they had all shown some improvement with increasing age

During the first year of life the patient began suffering with recurring bouts of feverishness followed by jaundice and pallor In the second year, abdominal pain and vomiting occurred with each attack From the third to the eighth year, at least four severe attacks a year were noted, there was increasing anorexia and fatigue and interference with normal activity

The salient features noted on examination were malnutrition and underdevelopment, moderate icterus of the skin and sclerae, pallor of the mucous membranes, enlargement of the heart with a loud hemic murmur, enlargement of the liver to four finger-breadths below the costal margin, and a palpable spleen reaching to the level of the umbilicus

The erythrocyte level was 2,600,000 per cubic millimeter, the hemoglobin 8 grams per cent, the reticulocytes 22 per cent, the red cells in the stained smears were predominantly microcytic and globular The icterus index was 40, the fragility of the red blood cells began at 0 78 per cent saline solution and was complete at 0 36 per cent, urobilinogen in the urine and the feces was increased to twenty times normal Roentgenograms revealed an increased porosity of the bones of the extremities and of the skull with widening of the marrow cavities, enlargement of the heart, and ossification of carpal centers corresponding to that of a child less than five years of age

Because of the typical findings of congenital hemolytic anemia and because a hemolytic crisis occurred shortly after hospitalization, splenectomy was advised This was refused by the parents During the following two years the attacks of hemolysis continued with increasing severity, requiring bed rest for a month at least four times a year Laboratory data showed no change, except for variations in the degree of anemia At the age of eleven years, abdominal pain began to be localized in the right upper quadrant and

ing the oxygen surrounding the cells with carbon dioxide The sickling trait may appear within a few minutes or may not appear for a variable time up to twenty-four hours In some patients, especially during the hemolytic crisis, sickling may be observed even in a rapidly dried blood film

The erythrocyte level is usually below normal and falls precipitately during a crisis, occasionally it reaches 1,000,000 erythrocytes per cubic millimeter or less In the chronic form of the disease the hemoglobin content of the cell is reduced There are signs of increased erythropoietic activity, with large numbers of polychromatophilic erythrocytes, reticulocytes, and even nucleated red cells The leukocytes are increased in number, especially during a crisis, and there is an increasing immaturity of the cells at this time The platelets may increase in number during a crisis

Plates 33 and 34 show the blood cells in sickle cell anemia

In the interval between attacks, if sufficient time elapses, the numbers of erythrocytes and leukocytes return to normal However, the sickling tendency of the red cells persists

There is an increased amount of bilirubin in the serum, producing an elevated icterus index and an indirect Van den Bergh reaction The fragility of the erythrocytes in hypotonic saline solutions is somewhat increased

The urine and feces show an excessive excretion of uribilinogen, especially during and after hemolytic crisis

In the child with the chronic form of sickle cell anemia, the bone marrow becomes hyperplastic, producing widening of the marrow spaces with a consequent thinning of the cortex and increased trabeculation Roentgenograms show greater radiability of the skeletal structures, particularly in the skull, the long bones, the hands and feet These changes are similar to those found in other chronic forms of hemolytic anemia

Diagnosis Sicklemia should be considered in every patient of the Negro race who has had repeated attacks of jaundice, weakness, and pallor Pallor and jaundice may be difficult to detect in a deeply pigmented skin but the diagnosis is readily substantiated by the finding of sickle cells in the peripheral blood smears The occurrence of fever and of pains in the joints, especially when associated with

The sickling phenomenon is said to depend upon an heredita defect in the function of the bone marrow with the production potentially deformed cells However, the change in the shape of t cells is brought about by *variations in oxygen tension, both with* and outside the body It has been suggested that the development anemia in an individual with the sickling trait may be precipitate by acute or chronic infection, by disturbances in the blood plasma in the rate of vascular flow through the capillaries, or by increase hemolytic activity of the spleen or other reticulo endothelial tissu

Symptoms and Signs The early symptoms are recurrent attac of weakness, fatigue, anorexia, abdominal pain, icterus of the sclera and pallor In young children, there may be vomiting and fever the onset of each attack The symptoms vary in degree and becom most severe when a hemolytic crisis is precipitated, as occurs fr quently after an acute infection Arthritic manifestations are n uncommon Sharp pain referred to the left upper quadrant of th abdomen may be significant of infarcts in the spleen In childre ulcers of the legs, so commonly described in adults with chronic sick cell anemia, are rare

Examination during or shortly after a hemolytic crisis reveals a icteric tinge to the sclerae, increased pallor of the lips and mucou membranes, enlargement of the liver and spleen, enlargement of th heart with hemic murmurs, tenderness and spasticity of the abdom nal muscles, elevated temperature, and increased pulse and respira tory rates

Between attacks the patient may show only anemia, a sub-icter tint to the sclerae, and little or no enlargement of the spleen Histo logically the spleen is the seat of numerous small hemorrhages situate usually around Malpighian bodies Replacement of the foci o hemorrhage by deposits of calcium and iron, and subsequent ingrowt of connective tissue, is accompanied by diminution in the size of th spleen Most of the changes in the tissues, such as extramedullar hematopoiesis, hemosiderosis, and hyperplasia of the bone marrow are dependent upon the severity of the anemia

Laboratory Data The characteristic sickle cell may be demon strated in a properly prepared fresh blood film—namely, a film from which the air is excluded by sealing with oil or vaseline, or by replac-

Erythroblastosis Fetalis or Hemolytic Anemia of the Newborn

These terms are used to describe a disease occurring late in fetal life or shortly after birth, in which excessive destruction of the erythrocytes takes place and the bone marrow, the liver, and the spleen are extensively overcrowded with centers of erythroblastic tissue The peripheral blood often reflects this by the presence of numerous nucleated red cells, while anemia develops from the excessive hemolysis Edema, jaundice, and extreme pallor may be observed either singly or in combination For this reason the disease has also been described under the names of universal edema of the fetus or fetal hydrops, familial icterus gravis, and congenital anemia of the new born

Etiology In 1941, Levine and his co workers discovered an abnormal hemagglutinin in the serum of mothers of infants with erythroblastosis fetalis This antibody agglutinated the red blood cells of the infant and of the father as well A factor was thereby identified in the erythrocytes of the infant and of the father which was lacking in the mother By parallel tests with an anti rhesus serum produced in rabbits by Landsteiner and Wiener in 1940, Levine showed that this blood factor was closely related to the Rh agglutinogen found in 87 per cent of the white population These mothers belonged to the 13 per cent who lack this agglutinogen and are therefore termed Rh negative

Levine postulated, and he as well as other investigators have proved, that in most instances the bases for the development of erythroblastosis fetalis are the immunization of the Rh negative mother by the Rh positive red cells of the fetus*, the production by her of an anti Rh agglutinin, the passage of this soluble substance into the circulation of the infant, the destruction of fetal erythrocytes after specific reaction with the anti Rh agglutinin The result was the development of jaundice, anemia, and all the other signs and symptoms of this disease

As to the heretofore unpredictable incidence of the condition in any

* In a few instances it has been shown that the mother developed the anti Rh agglutinin as the result of previous transfusions with Rh positive blood cells

an enlarged heart and hemic murmurs, may suggest rheumatic fever. Abdominal pain, with tenderness and rigidity of the muscles, may simulate an acute surgical disease. Roentgenological changes similar to those observed in the bones of patients with sickle cell anemia are likewise found in children with congenital hemolytic anemia and with Mediterranean anemia. However, there should be little difficulty in differentiating these diseases since the clinical and hematological findings are so dissimilar.

Course and Prognosis. These vary with the severity of the sickling tendency, the frequency and duration of the crises of hemolysis, and the age of the patient. The younger individuals fare less well, for recurrent severe anemia often interferes with proper growth and nutrition, thus restricting the general activity of the patient. Death may result from rapidly developing severe anemia or intercurrent infection. In the chronic forms of the disease the spleen may gradually diminish in size over a period of years as fibrosis and contraction of this organ take place.

Treatment. Splenectomy has been advised for the patient with severe chronic sickle cell anemia. The spleen plays an important role in the destruction of blood, and its removal has been followed by diminishing hemolysis and anemia. However, some doubt has been entertained regarding the value of operative interference, since the sickling trait may not be altered thereby and the lymph nodes and other reticulo-endothelial tissue may continue the active phagocytic function of the spleen. Intercurrent infection must be avoided and foci of infection eradicated since either may precipitate a hemolytic crisis. Between attacks of hemolysis, preparations of liver may be beneficial as an aid in stimulating rapid recovery from the anemia.

Transfusion remains the best mode of symptomatic relief from the anemia as well as the hemolytic tendency. It has been shown that not only is the blood level restored by this procedure but, since normal blood plasma contains protective bodies against the hemolytic process, the hemolytic crises may thereby be reduced in frequency or entirely eliminated. For this purpose it is preferable to use, as needed, repeated transfusions of small amounts of whole matched blood.

the infant with the disease This is discussed below, in the section on treatment of this condition

Symptoms The symptoms and signs may be explained on the basis of excessive hemolysis, abnormal activity of blood production, and interference with the normal function of the organs that are the sites of extramedullary hematopoiesis and hemosiderin deposits, chiefly the liver and the spleen Profound anemia is constantly found, and in the first few days the peripheral blood contains large numbers of immature cells, chiefly of the red cell series Universal edema and general anasarca are usually found only in those infants dying before or shortly after delivery Jaundice may be present at birth or become apparent shortly thereafter The placenta may be either normal in size or considerably enlarged The vernix may be either normal in appearance or dark yellow Increasing icterus often masks the developing pallor which rapidly increases after the third day of life Petechiae, ecchymoses, and free bleeding occasionally occur in the first few days The spleen and the liver may be palpable at birth or become greatly enlarged in the first week of life Enlargement of the heart with hemic murmurs may develop Respiratory embarrassment and tachycardia may dominate the clinical picture and focus attention on the cardio respiratory system alone If the jaundice becomes very intense, staining of the nuclei of the brain, or kernicterus, may occur Drowsiness and convulsions are seen as a terminal event in such infants If the icterus is mild or fades rapidly the pallor of the skin and the mucous membranes becomes more apparent

Laboratory Data In the early stages of the disease the outstanding characteristic is the great increase in the number of nucleated erythrocytes in the peripheral blood In contrast to the premature or full-term infant who for the first two days may have from 200 to 2,000 nucleated red cells per cubic millimeter, the infant with erythroblastosis usually shows from 10,000 to 100,000 nucleated erythrocytes within the first forty eight hours of life In addition to these immature cells, there are also large numbers of reticulocytes, red cells with nuclear fragments, and other evidences of immaturity The erythrocytes are macrocytic and are well filled with hemoglobin, and the color index is greater than unity There is little variation in the shape of

family, this is now clarified in a large part by the genetics of the Rh blood factor, which is inherited as a dominant trait The offspring of an Rh-positive father and an Rh-negative mother will be Rh positive in 100 per cent of cases if the male is homozygous, i e, genotypically he has two dominant genes, RhRh If the male is heterozygous and carries one dominant and one recessive gene, or Rhrh (rh indicating the absence of the Rh factor), only 50 per cent of the offspring will be Rh-positive The immunization of the mother presumably occurs slowly, usually one or more pregnancies with an Rh positive fetus is necessary for the development of a sufficient amount of anti-Rh agglutinin to harm the fetus Two other conditions are postulated as prerequisite to the development of this agglutinin (1) fetal Rh-positive blood elements must get through the placenta and enter the maternal circulation (the placenta should ordinarily be impervious to formed elements), (2) the mother must be capable of producing the agglutinin (not all humans are antibody-producers)

Were these limitations not operative, the incidence of this disease, usually given as about one in 200 births, would be much higher, for the mating of an Rh-positive male with an Rh-negative female occurs about eleven times in a hundred Still another limitation to the theoretically greater incidence of erythroblastosis fetalis is the present tendency toward small families, for the possibility of the development of a strong anti-Rh agglutinin and the subsequent birth of erythroblastotic infants is greatly increased after the first or second pregnancy This accounts for the frequent "escape" of the first and even the second Rh-positive offspring

It has been found that about 90 per cent of the cases of erythroblastosis fetalis can be resolved on the basis of iso-immunization with the Rh group The remaining 10 per cent may and in some cases have been proved to involve other unusual blood factors or even the common agglutinogens, A and B, when an incompatible mating occurs

The therapeutic implications of this discovery of iso-immunization in humans are the necessity for, first, searching for abnormal agglutinins in recipients of blood transfusions, especially women during and after gestation, and using only blood compatible by every method of typing, i e, for Rh as well as A and B groups, and, second, giving transfusions of suitable blood, least likely to be destroyed quickly, to

immediately or within two weeks following delivery After this time, it tends to disappear rapidly The demonstration of this antibody is indisputable proof of the diagnosis In rare cases, some of this agglutinin may be identified in the infant s serum shortly after birth

Diagnosis A familial incidence, the early appearance of icterus, possible edema, numerous erythroblasts and normoblasts in the peripheral blood, as well as a general macrocytosis and anemia, occasionally bleeding phenomena, enlargement of the liver and spleen, and an enlarged placenta and yellow vernix suggest the diagnosis of erythroblastosis fetalis To be ruled out are first and foremost, congenital syphilis, since it may produce many of the signs mentioned above, other ante natal or early post natal infections, such as colon bacillus sepsis, streptococcus and staphylococcus aureus bacteremia, congenital malformations of the liver or the bile ducts or of other organs or systems of the body, although in these the erythroblastosis and severe anemia are seldom seen, traumatic or spontaneous hemorrhage in the newborn with severe anemia and secondary erythroblastosis, primary blood diseases such as aplastic anemia, congenital hemolytic jaundice, thrombocytopenic purpura, and leukemia, even though these diseases are extremely rare at this age The diagnosis should not be confused by the presence of the immature red cells which for the first few days are usual in small numbers in the blood of premature and normal full term infants

Course and Prognosis The appearance at birth or shortly thereafter of edema, jaundice, and anemia constitutes evidence of the most severe form of erythroblastosis fetalis and unless promptly recognized and treated a fatal termination may result If edema is absent and jaundice and anemia develop more gradually in the first or second day of life, the infant may survive, especially if transfusion is given early and as frequently as is necessary After the first week, the hemolytic tendency diminishes and thereafter transfusion is not required so frequently Only rarely is it necessary in the second month Several weeks may elapse before normal hematopoiesis is established, improvement as evidenced by reticulocytosis begins usually at four to six weeks Normal erythrocyte and hemoglobin levels may be expected by the end of the fourth month, and thereafter the infant continues well

the cells Only in the severe forms is there more than a slight degree of anemia in the first twelve hours of life, but as the disease progresses the erythrocytes decrease very rapidly, sometimes by as much as a million per cubic millimeter per day, and a profound anemia may ensue by the third or fourth day The nucleated erythrocytes tend to diminish and may even disappear entirely at the end of this time, their absence should not confuse the diagnosis The macrocytosis persists throughout the active stages of the disease and is one of the diagnostic criteria not to be overlooked

The leukocytes number from 15,000 to 30,000 per cubic millimeter, and immature forms of granulocytes and lymphocytes predominate

In severe forms, the platelets are generally greatly reduced in number in the first few days (See Plates 13, 14, 15, 16, and 17) The bleeding time, therefore, tends to be greatly prolonged A prothrombin deficiency may be present to augment this bleeding tendency After the first week the platelets return to normal levels and then the bleeding tendency subsides

The icterus index is generally high immediately after birth and tends to increase to a hundred or more within the first week The Van den Bergh test yields a direct as well as an indirect reaction The fragility of the erythrocytes in hypotonic saline solutions shows a slight increase in the concentration at which hemolysis begins and a decrease at its termination, a state usually described as an increased resistance

Between the sixth and twelfth days it is not unusual for the feces to become clay colored and the urine bile tinged This acholic state lasts only a few days or weeks During active hemolysis, both the urine and the feces show increase in the amount of urobilinogen excreted

The Hinton test is invariably negative

Typing of the blood for the Rh factor has become very important for both diagnostic and therapeutic reasons By the use of anti Rh serum, according to the method of Levine, the red cells of the infant are found to be Rh-positive, as are the father s, whereas the mother s are Rh negative (the exceptions to this finding are discussed under *Etiology*) If, in addition, the mother s serum is tested for an anti-Rh agglutinin, in about a third of all cases it may be present, either

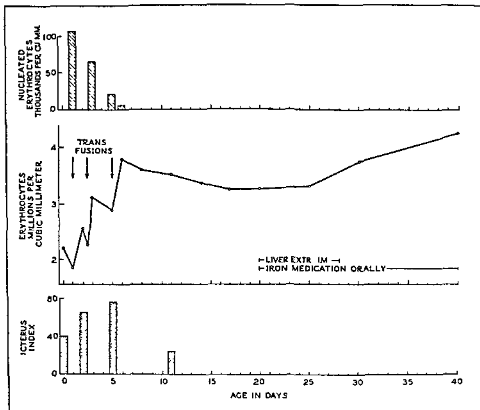


CHART 17 Erythroblastosis fetalis or hemolytic anemia of the newborn icterus gravis type This third offspring the second infant in the family with the disease was jaundiced at birth Shortly after birth severe anemia was discovered and the nucleated red cells were found to number 100 000 per cubic millimeter Rapid improvement followed transfusion with Rh negative blood and the infant was discharged home on the twentieth day of life Because of the low level of reticulocytes four intramuscular injections of liver extract were given in the next week and oral iron medication was prescribed until the fortieth day by which time the blood levels had reached normal values for the age

Intramuscular injection of blood is undependable—if it is of any value The use of blood serum or plasma in place of whole blood is of questionable value Liver or liver extract, even parenterally administered, has proved to be of very doubtful benefit early in the disease Later, in the recovery period, liver administered parenterally may hasten the appearance of a satisfactory reticulocytosis Medicinal iron by mouth is of assistance in hastening improvement (see Chart 17)

In the first twenty-four hours, especially if icterus and anemia rapidly increase, the outlook is grave Each day of life adds to the probability of improvement If the icterus develops slowly and anemia is not rapidly progressive, early treatment leads to complete recovery The disease tends to undergo spontaneous remission which begins usually by the fourth to eighth week of life The anemia rarely lasts as long as three to four months, especially if transfusion is repeated frequently Kernicterus with impairment of the central nervous system is a rare but serious sequel

Treatment Early treatment should be directed toward the maintenance of the blood at a satisfactorily functioning level until normal hematopoiesis begins The method of attaining this state is by the intravenous injection of properly matched whole blood, the amount and frequency being determined by the degree of anemia or by the general condition of the patient

Since the demonstration of the role of the Rh factor in the etiology of this disease, it has become important that Rh negative blood be used in transfusing the infant whose mother is Rh-negative, especially during the first two weeks of life Theoretically, the infant s circulation may contain some uncombined anti-Rh agglutinin derived from the mother, and this may react with and decrease the usefulness of Rh-positive blood cells used for the transfusion Practically, it has been found that Rh positive blood, especially from the donor most commonly used, the father, must be given more frequently and in larger amounts than expected during the first two weeks of life in order to maintain the erythrocytes at a satisfactory level Blood from a previously tested compatible Rh-negative donor is therefore most satisfactory and produces the speediest improvement (see Chart 17) It is inadvisable to use whole blood from the mother to transfuse her infant, for this may add more anti-Rh agglutinin and destroy more of the infant s erythrocytes In a few instances where such blood was used before the Rh factor was discovered, a marked increase in anemia and in jaundice was noted (see Chart 18) Recently, however, when a tested Rh-negative donor has not been available, the mother s blood has been used, but only after first removing the plasma and washing the erythrocytes with normal saline and then resuspending them in saline before injection

CASE RECORD ERYTHROBLASTOSIS FETALIS

A ten hour old white female infant was brought to the hospital because of icterus of the skin and sclerae and pallor of the lips

The family history was important in that there had been seven previous pregnancies The first four children had been normal throughout infancy, but the three succeeding pregnancies resulted in infants who developed jaundice and anemia during the neonatal period

The eighth pregnancy was uneventful until three days before term At this time, the mother felt that fetal movements were very infrequent and weak, whereas activity had been great previously She recalled that she had felt a sudden lack of fetal movements about three days before term in the preceding three pregnancies The fetal heart sounds were noted by her physician to be normal At term, a female infant weighing five pounds twelve ounces was delivered normally She appeared somewhat limp but breathed well No observations were made on the amount or character of the amniotic fluid The placenta was said to have been large At five hours of age there seemed to be definite pallor and slight icterus, as well as many fine black and blue spots over the body of the infant

Admission examination showed a small lethargic infant, with marked icterus of the skin and sclerae and pallor of the mucous membranes There were numerous petechiae over the face, body, and extremities The heart was somewhat enlarged to percussion A blowing systolic murmur was present over the precordium The spleen reached almost to the iliac crest, and the liver was palpable four centimeters below the costal margin

Examination of the blood at this time showed an erythrocyte level of 1 700,000 per cubic millimeter and hemoglobin of 6 grams or 38 5 per cent The total nucleated cell count was 90,000 per cubic millimeter but only 20,000 of these were leukocytes The platelets were diminished to 80,000 per cubic millimeter Examination of the stained smears of the blood showed a striking macrocytosis with large numbers of nucleated erythrocytes The bleeding time was prolonged to fifteen minutes the icterus index was 40, the Hinton test was negative

An immediate transfusion of matched whole blood from the father was followed by a rise in the erythrocytes and diminution in the bleeding time Petechial hemorrhages ceased to appear The icterus, however increased in intensity On the third day the erythrocyte count had diminished once more to under 2,000,000 per cubic millimeter and the bleeding time was again prolonged At this time too there was definite edema of the eyelids, pitting edema of the lower extremities and slight edema of the hands Another transfusion was given with apparent improvement Because of the prolonged bleeding time and a slightly bloody discharge from the vagina and the persistent icterus and edema, two small transfusions were given on the

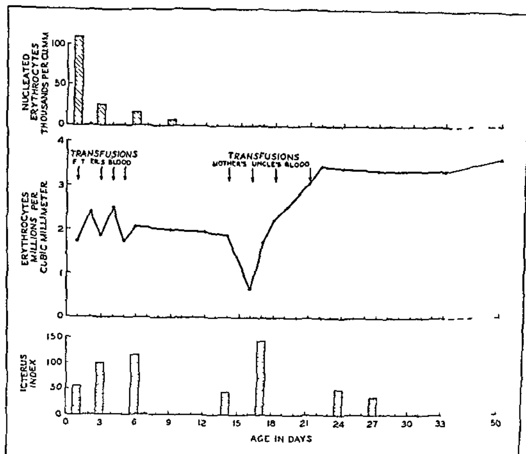


CHART 18 Erythroblastosis fetalis or hemolytic anemia of the newborn icterus gravis type This infant the fourth in a family in which two previous children were similarly affected, was deeply jaundiced at birth and severely anemic at two days of age The father was used as the donor for the first four transfusions The infant s general condition improved but the red cells were not maintained at the expected level after each transfusion and the jaundice increased considerably On the fourteenth day the icterus index had diminished but the erythrocytes numbered only 2,150 000 per cubic millimeter The infant was given a transfusion of two ounces from the mother whose blood was of the same group there was an immediate fall in red cells, to a level of 1,000 000 on the sixteenth day and a sudden increase in icterus index Fortunately the maternal uncle was a compatible donor and the injection of three 90 cc amounts of his blood was followed by speedy improvement in the baby s blood levels and eventually by complete recovery Analysis of this family s blood groups four years later (1941) disclosed that the father was Group O Rh positive and all his children including the patient were the same The mother was Group O Rh negative and her serum contained a moderate titer of anti Rh agglutinin The maternal uncle was Group O Rh negative This accounted for the unexpected fluctuations in the red cell levels following transfusions

The spleen was enlarged two finger breadths below the costal margin as was the liver

Blood examination revealed an erythrocyte level of 1,200,000 per cubic millimeter, a hemoglobin of 4 7 grams or 30 per cent, and a leukocyte count of 14,000 per cubic millimeter Stained blood films showed marked macro cytosis, with more than 10 per cent reticulocytes and 10 nucleated erythro cytes in each hundred nucleated cells The platelets were normal and only occasional myelocytes and young neutrophils were found The icterus index was 15 The Hinton test was negative

Transfusion of matched whole blood from the father was given on the fourteenth and fifteenth days of life (60 cubic centimeters each day) The erythrocyte level had risen to 3 400,000 per cubic millimeter on the sixteenth day of life and no nucleated erythrocytes or reticulocytes could be found on examination of the stained blood films The child continued to eat well and gain in weight, permitting discharge home on the twenty fourth day of life when the erythrocytes numbered 3,000,000 per cubic millimeter and reticu locytes were 6 per cent

When the infant was re examined on the fortieth day, the color had improved, no heart murmur was heard, the spleen was barely palpable, and the liver was enlarged only three centimeters below the costal margin The erythrocyte level was 3 800 000 per cubic millimeter the hemoglobin 8 6 grams or 55 per cent, the leukocytes numbered 8,200 per cubic millimeter and the stained blood smears showed normal cells for this age with 4 per cent reticulocytes

Subsequent tests of the blood groups of the members of this family showed that the father was group O Rh positive both children were group O, Rh-positive, the mother was group A, Rh negative No anti Rh agglutinin was demonstrable in her serum forty days after delivery

Comment This exemplifies the type of erythroblastosis fetalis commonly described as congenital anemia of the newborn Although in retrospect it was thought that the amniotic fluid had been darker than normal at birth, this and the early appearance of jaundice were not evaluated as signs of possible abnormality in the infant The pallor became more noticeable toward the end of the second week, as so often occurs when the jaundice fades At entry to the hospital, the infant showed marked pallor, enlarge ment of the spleen and of the liver A loud heart murmur of hemic origin, judging by its later disappearance, was heard The blood examination revealed a profound anemia, with a striking macrocytosis The nucleated erythrocytes were not sufficiently numerous to be more distinctive of eryth roblastosis fetalis than of hyperactivity of the bone marrow following any severe anemia The high level of erythroblasts found in this disease com monly disappears by the second week of life or even earlier

sixth and seventh days On the twelfth day, bleeding from the umbilical cord occurred, it was controlled by another transfusion (the fifth) At this time, the edema had disappeared, the icterus was very faint, the color had improved, the liver was barely palpable, and the spleen reached two to four centimeters below the costal margin Steady improvement continued until discharge on the eighteenth day of life

At the age of two months, the patient had gained in weight and grown satisfactorily, the spleen was barely palpable, and the erythrocyte level was 2,800,000 and hemoglobin 8 grams per 100 cubic centimeters of blood At three and one-half months, with continued improvement in the child s growth and development, the erythrocyte count was 3,800,000 and the hemoglobin level 11 grams When seen finally at three years of age, the child appeared normal in physical growth as well as in intellectual attainments The erythrocyte level was 5,100,000, and the hemoglobin 15 4 grams

Comment This infant exhibited, *shortly after birth, the diagnostic criteria* for erythroblastosis fetalis The family history was of great importance since three previous children had likewise had jaundice and anemia shortly after birth Following five transfusions given during the first twelve days, the patient began to improve and thereafter made a satisfactory recovery The course exemplifies the type of severe erythroblastosis fetalis associated with slight edema, severe jaundice, and profound anemia which with prompt and continued treatment may respond satisfactorily

CASE RECORD ERYTHROBLASTOSIS FETALIS (MILD)

A white female infant was admitted to the hospital on the fourteenth day of life, because of marked pallor The parents were in good health and there had been one previous pregnancy resulting in a healthy child who *had been entirely well*

At the time of the delivery, it was noted that the placenta was normal in size but that the amniotic fluid seemed dark colored The infant appeared well, although slight jaundice was noted on the second day becoming more marked by the fourth day but fading thereafter so that it was hardly visible by the thirteenth day The baby took her feedings well and gained weight On the thirteenth day, the mother expressed apprehension regarding her infant s obvious pallor On the next day, the family physician confirmed the marked pallor, estimated the hemoglobin level as less than 40 per cent, and advised further hospital care

Physical examination revealed a normal appearing infant, vigorous and active, but markedly pale There was no visible jaundice of the skin or sclerae, no petechiae or ecchymoses or obvious source of blood loss The heart rate was rapid and a murmur was audible throughout the precordium

III. The Leukocytes in Disease

As has been stated in Chapter I, the total number of leukocytes per cubic millimeter of blood varies with the age of the individual (see table, page 8). Furthermore, the percentage distribution of the various types of leukocytes and their state of maturity change with age. For example, in the newborn the number of white cells may rise to about 20,000 per cubic millimeter for the first two to three days. At this time the predominating cells are myeloid, most of them being the young forms of polymorphonuclear neutrophils, but even myelocytes and myeloblasts may be found. The total number of leukocytes, the high percentage of myeloid cells, and the number of immature forms all diminish rapidly within the first two weeks after birth. A leukocyte level of about 10,000 per cubic millimeter is established after the second week and is maintained with slight variations throughout the first three to six months. The percentage of lymphocytes increases so that a relative lymphocytosis exists. Between the first and sixth years of life, the leukocyte level diminishes slowly to that usually considered normal for the adult (about 8,000), and the percentage of lymphocytes falls until a slight neutrophilic leukocytosis exists; this condition is maintained up to and throughout adult life in normal health. The number of young forms of cells also gradually diminishes so that after six years of age there are very few immature cells of any type.

LEUKOCYTOSIS AND LEUKOPENIA

Leukocytosis may be defined as that state in which the total number of circulating leukocytes exceeds the normal for the age. The increase may be due to an increase in any one of the different types of leukocytes, the most common type being an increase in polymorpho

Following transfusion of matched blood, the infant made a rapid recovery In the ensuing week, normal erythrocyte regeneration began, as judged by an increase in reticulocytes, and by the sixth week the blood levels had almost returned to their normal state

The blood typing of this family revealed the absence of the Rh factor in the mother's erythrocytes and its presence in the father's and children's—the prerequisite state for iso immunization of the mother and consequent development of erythroblastosis fetalis in the baby

piratory infections which are commonly associated in other patients with an increase in the number of neutrophilic cells

At the onset of the ordinary type of acute infection with a neutrophilic leukocytosis there is usually a decrease in lymphocytes, in monocytes, and in eosinophils As the infection progresses beyond the acute stage and healing begins, the neutrophils may begin to diminish and a monocytosis may be present for a relatively short time During convalescence the neutrophils may diminish still further with an increase in eosinophils and lymphocytes The recognition of this orderly progression and of the changes in the relative percentages of the various forms of leukocytes not only prevents error in diagnosis but also assists in prognosis

NEUTROPHILIC LEUKOCYTOSIS

A neutrophilic leukocytosis may occur in response to a number of causative agents, the most important of which are chemical agents, acute hemorrhage, and infection resulting from many of the pathogenic organisms and their products (See Plate 35)

In addition to the total number of neutrophils per cubic millimeter of blood, significant information may be obtained by considering the state of maturity of the cells, remembering that the neutrophils may exhibit increasing immaturity as disease progresses The level of the leukocytosis is of some diagnostic value as an indication of the degree of activity of the underlying process A diminution in the leukocyte level usually signifies improvement, although it may represent an exhaustion of the reserve of leukocytes in the bone marrow Plates 2 and 3 illustrate that the neutrophil arises in the bone marrow from a myeloblast and passes through various stages of maturity of myelocytes to its mature form the polymorphonuclear neutrophil Examples illustrating immaturity of the neutrophils in infection are shown in Plates 36, 37, and 38

Toxic granules are often seen in the neutrophils in severe infection These granules appear larger and more basophilic and are widely scattered, in contrast to the fine, evenly stained, densely packed neutrophilic granules of the normal cell (See Plates 36, 37, and 38)

A further index of severe infection may be found in vacuolization

nuclear neutrophils If the increase is in *lymphocytes it is termed* lymphocytosis, if in eosinophils it is called eosinophilic leukocytosis or eosinophilia, if in monocytes, monocytosis

Leukopenia represents a decrease in the total number of circulating leukocytes, below the normal for the age If it involves chiefly the polymorphonuclear neutrophils, it is termed neutropenia or granulocytopenia If the lymphocytes are chiefly affected, it is termed lymphopenia

Because of the importance attached to variations from the normal in the number of leukocytes in the circulation, it is essential to appreciate the limits of normality not only for any given age but also for any given individual Fluctuations may normally occur in the leukocyte level as the result of physiologic processes For example, it has been demonstrated by Sabin and her co-workers that there occurs daily a so called diurnal tide' of leukocytes and that at two periods during the day, usually late in the morning and late in the evening, there is a physiologic leukocytosis with intervening periods of relative leukopenia *These changes apparently affect the total number of cells* and are not restricted entirely to neutrophils as would be the case in a leukocytic response to bacterial infection Likewise, it has been shown that the ingestion of food influences the number of circulating leukocytes, though the exact mechanism is not clearly understood Other factors which may alter the leukocyte level are muscular activity, rest, body temperature, and altitude

When these normal variations in leukocyte level have been excluded, an alteration in the number of white cells may be considered pathologic " Careful consideration of the meaning of such alterations may assist materially in diagnosis, prognosis, and treatment of disease

In addition to fluctuation with age, the correct interpretation of the number of leukocytes and the type of cell reaction requires an understanding of such factors as differences in the reaction of various individuals to the same type of infection, and differences in the reaction of the blood in succeeding stages of the infection One patient may develop a neutropenia with the same type of infecting organism that induces neutrophilic leukocytosis in another patient Some children exhibit a lymphocytosis in response to ordinary res-

EOSINOPHILIC LEUKOCYTOSIS OR EOSINOPHILIA

The normal number of circulating eosinophils varies between one and two per cent of the total leukocytes or, in absolute numbers, from 100 to 200 cells per cubic millimeter. An increase up to 5 to 10 per cent may be found in certain infectious diseases such as scarlet fever in its early stages and also in the healing stages of acute infections. However, an eosinophilia of 10 per cent or above (in absolute numbers more than 1,000 cells per cubic millimeter) is an important diagnostic sign in so-called allergic diseases such as asthma, hay fever, angioneurotic edema, and urticaria. This is illustrated in Plate 39. Not only are these cells increased in the peripheral blood but the nasal and oral secretions of allergic patients also show an eosinophilia.

Eosinophilia is likewise found in infection caused by intestinal parasites such as hookworms, tapeworms, roundworms, and occasionally even pinworms. Likewise, eosinophilia may be present in amebiasis and filariasis as well as in trichiniasis after the cysts have formed in the muscles. Finally it may occur to the greatest degree as the peculiar response of certain individuals to low-grade chronic infection. This type of reaction is said to occur in families. It is illustrated by Plate 40, portraying the blood of an individual who constantly showed an eosinophilia of over 60 per cent of a leukocyte level of 30,000 to 40,000 associated only with severe chronic sinusitis. Such a reaction may persist for a month or even for more than a year, but generally it abates with improvement in the general condition of the patient.

LYMPHOCYTOSIS AND LYMPHOPENIA

The absolute and relative number of lymphocytes varies within wide limits at different age periods throughout the early years of life. Following the neutrophilic leukocytosis that is present at birth, the neutrophils decrease and the lymphocytes increase, so that after the tenth day the lymphocytes constitute over 50 per cent of the white cells. They remain at this level throughout most of the first two years of life, then, after the second year they decrease gradually until at six years the figure normal for the adult is reached (see table, page 8).

of the cytoplasm of the neutrophils This generally occurs in overwhelming and rapidly progressive infection, particularly with bacteremia or septicemia In such instances it is common to find, in addition to vacuolization, toxic granulation of the cytoplasm, increasing immaturity of the neutrophils with even myelocytes in larger percentages, and, terminally, a falling leukocyte level This, too, is illustrated in Plates 36, 37, and 38 Vacuolization of the cytoplasm not infrequently occurs in the blood of patients with severe and extensive burns

NEUTROPENIA

A leukopenia with a relative decrease in the number of neutrophilic cells may suggest, as has been mentioned, an overwhelming or prolonged infection In addition, certain chemical substances may cause neutropenia, particularly benzol and its derivatives, aniline, arsphenamine, dinitrophenol, amidopyrine, and many varied proprietary combinations of these drugs Neutropenia may be associated with inflammation and ulceration of the buccal mucous membrane in the mouth and throat, as in agranulocytic angina or malignant neutropenia which fortunately is extremely rare in childhood Radiation with roentgen rays or radium or radioactive substances likewise may so injure the bone marrow as to produce a neutropenia

Neutropenia may be of diagnostic significance in a variety of diseases In such diseases the leukocyte level is seldom less than 3,000 cells per cubic millimeter The neutrophils are usually moderately to slightly decreased in relation to the other cells Such leukopenia occurs in measles, German measles, roseola infantum, mumps, influenza, malaria, undulant fever, typhus fever, typhoid fever, and occasionally in bacillary dysentery

A leukopenia with a diminution of neutrophils may be observed as part of a generalized depression of the blood cells, involving not only the leukocytes but also the erythrocytes and the thrombocytes, in diseases such as aplastic anemia and leukemia or other malignancies invading the bone marrow

The incubation period is said to be between five and twelve days The degree of contagiousness is so low that, except during epidemics, a stated quarantine period is not usually carried out

Symptoms and Signs The generalized enlargement of the lymph nodes is the outstanding and most constant clinical feature The lymph nodes rarely fail to show enlargement when there are typical cells in the blood smear The adenopathy usually begins and reaches its maximum in the cervical region The axillary and inguinal nodes are enlarged in most instances, and the epitrochlear nodes also may be palpable The spleen is enlarged in about half the cases An acute inflammation of the throat occurs in over 75 per cent of patients Frequently there is swelling of the lymphoid tissue of the nasopharynx with a granular pharyngitis Occasionally there is a membranous angina and the buccal mucous membranes become ulcerated and covered with exudate Fever may mount to more than 103 F, and malaise, headaches, pains in the joints, sweating, and chills occur especially in older children Swelling of the mesenteric lymph nodes occasionally produces abdominal pain with nausea and vomiting and in rare instances even obstruction of the bile ducts

Laboratory Data The erythrocytes, the hemoglobin, and the platelets are not affected Although the total number of leukocytes is often increased, the disease may be ushered in by a leukopenia During the period of enlargement of the lymph nodes, a leukocytosis develops with a level of about 20,000 cells per cubic millimeter Rarely at the height of the disease the leukocytes number 50,000 for a short time About three weeks after the onset, the leukocytosis disappears

The differential cell count reveals an increase in mononuclear cells, including both monocytes and lymphocytes It is the latter that show the greatest relative and absolute increase, sometimes numbering more than 50 per cent of all the white cells This lymphocyte is an atypical form not usually seen in other diseases, which varies in its staining qualities in different patients The nucleus is often placed eccentrically, and the cytoplasm is basophilic In such cells a clear area may be seen at the indentation of the nucleus Occasionally, vacuoles and reddish-staining granules appear in the cytoplasm More frequently the cytoplasm is relatively large in amount, shaped irregularly, and squeezed in between adjacent red

In an acute or chronic infectious disease, a relative increase in lymphocytes may be considered as evidence of convalescence or satisfactory healing of the underlying morbid process. In hyperplasia of the lymphoid tissue and in iron deficiency anemia there is frequently a relative increase in lymphocytes. In this latter state, for example, with a leukocyte level of 10,000 cells per cubic millimeter, over 70 per cent of the cells may be lymphocytes. (See Plate 41.)

There are many diseases of known etiology in which leukopenia with a relative increase in lymphocytes can be used as an aid in diagnosis. Among these are typhoid and paratyphoid fever, typhus fever, dengue fever, influenza, malaria in its chronic form, tuberculosis in the healing stage, hereditary syphilis when associated with a lymphadenopathy, and the acute communicable diseases of childhood—measles, chicken pox, mumps, and roseola infantum.

Lymphocytosis is a characteristic feature in pertussis. In this disease the total number of white cells may range from 10,000 to 200,000 per cubic millimeter with a relative increase of lymphocytes to over 70 per cent. Although so high a level often suggests leukemia, the lymphocytes are reassuringly of the mature type. (See Plates 42 and 43.)

Lymphocytosis is also characteristic of infectious mononucleosis, although early in the course of this disease there may be transitory neutrophilic leukocytosis or even leukopenia.

Infectious Mononucleosis

This is an acute infectious disease characterized by fever, swelling and tenderness of the lymph nodes, often an enlarged spleen, and the appearance of atypical mononuclear cells in the peripheral blood. Synonyms are benign lymphadenosis and glandular fever.

General Considerations. The cause of the disease is not known. Many authors at present favor the theory of a filtrable virus that is lymphotropic in nature. The disease occurs not only sporadically but also in endemic and epidemic forms. In the latter form, youngsters of school age and students in preparatory schools and colleges, more often boys than girls, are afflicted. Infants rarely contract the disease.

course and duration cannot be predicted with certainty Relapses occasionally occur A slow convalescence is most common in older patients

Treatment There is no specific treatment for infectious mononucleosis, however, symptomatic therapy for the various complaints may make the patient more comfortable Proper nourishment, rest, and convalescent care may diminish the possibility of secondary disease

Isolation precautions are indicated only in epidemics such as occur in schools and colleges and among hospital staffs

CASE RECORD INFECTIOUS MONONUCLEOSIS

A boy, four and a half years old was brought to the hospital because of swelling of the lymph nodes of two weeks duration The family history and the past history were unessential He had appeared entirely well until two weeks before entry when the mother noted that his face seemed full At this time his physician found enlarged lymph nodes all over his body and his spleen palpable three finger breadths below the costal margin Up to one week before entry his temperature ranged from 102° to 103° F and then gradually fell to normal levels The child complained of abdominal pain and vomited once Six days before entry because of the persistence of the enlarged lymph nodes a biopsy was advised and the child was admitted to a local hospital An inguinal lymph node was removed and the presumptive diagnosis of lymphoma of the Hodgkin type was made The leukocyte level at this time was 20,000 per cubic millimeter with 50 per cent large mononuclear cells Two days before entry it was noted that the lymphadenopathy had begun to subside, and that the spleen had likewise diminished in size The patient felt well and had no further complaint

Physical examination revealed a well developed and well nourished boy with no evident pallor petechiae and jaundice were not present, there were moderate nut sized cervical lymph nodes and pea sized lymph nodes in the axillary and inguinal regions The heart and lungs were normal The spleen was palpable one finger breadth below the costal margin There was a scar of a recent incision in the left groin with sutures still present

Laboratory examination showed an erythrocyte level of 5,000 000 per cubic millimeter and hemoglobin 85 per cent The platelets numbered 240,000 per cubic millimeter and the leukocytes 15 000 In the stained smears of the blood there were 20 per cent neutrophils 34 per cent lymphocytes and 45 per cent large mononuclear cells with clear staining cytoplasm

cells In this type of lymphocyte, the cytoplasm tends to be light in its staining reaction and no granulation or basophilia is present In some instances the nucleus appears to contain multiple nucleoli, but careful observation shows these are small "holes' throughout the nucleus, or "nuclear fenestrations' These abnormal cells may not disappear completely from the peripheral blood for many weeks (See Plates 44, 45, and 46)

The only other measurement of significance is the high heterophile antibody content of the blood serum which appears two or more weeks after the onset of the disease Ordinarily a titer higher than one part in 32 is not found in normal individuals or in patients with other disease entities except serum sickness In infectious mononucleosis the antibody titer of the serum measured against sheep cells ranges from one part in 64 to one part in 4,000 or more A dilution above one part in 64 is therefore considered of diagnostic significance when unassociated with serum sickness The titer usually remains high for several weeks and then gradually recedes, becoming normal in about six months

Diagnosis Because of the frequent presence of large numbers of unusual cells, infectious mononucleosis is sometimes mistaken for leukemia Such an error leads to needless apprehension, since the disease is usually benign The normal state of the erythrocytes and of the platelets and the absence of immature 'blast' forms are reassuring distinguishing characteristics If doubt exists, biopsy of an enlarged lymph node may serve as the final means of differentiation between this disease and a malignant condition

Gall and Stout found, as prominent features of the histologic picture in the lymph node, preservation of the normal architecture, proliferative activity in the pulp which obscures the margin of the follicles, extensive but focal proliferative activity of clasmatocytes, and, most important, the presence in the pulp sinuses and at the periphery of germinal centers of large numbers of the specific infectious mononucleosis cells identical with those found in the circulating blood

Course and Prognosis The prognosis is favorable Complications are rare and fatalities result chiefly from intercurrent disease The

products A similar reaction occurs in infants and children suffering from active progressive tuberculosis, in which disease there may be a monocyte level as high as 10 to 20 per cent with a leukocytosis of 15,000 cells or more per cubic millimeter It should be pointed out that in active tuberculosis the monocytes may appear in modified or epitheloid form, and, though they can be recognized in the dry film, they are most correctly delineated by the supravital technique The increase in monocytes parallels the extension and activity of the tuberculous process and invariably is associated with a fall in the level of lymphocytes As healing takes place the level of monocytic cells decreases and the level of young lymphocytes rapidly increases As Sabin suggested, the ratio of monocytes to lymphocytes is a valuable index to diagnosis and prognosis in a given patient The increase in monocytes in tuberculosis and the change in type of cell are illustrated in Plates 47 and 48

Lipid laden monocytes are occasionally present in the circulating blood of patients exhibiting disorders of the lipid metabolism, such as Pick-Niemann s disease and related conditions (See Plate 49)

A mononuclear cell which Sabin derives from the endothelium rather than from the reticulum (which is ordinarily thought to give rise to blood monocytes) has been named the endothelial phagocyte or clasmatocyte This cell ordinarily remains in the tissues and only occasionally is found free in the blood circulation Usually its appearance there is in association with bacteremia, for it is the most active cell in the phagocytosis of particulate matter Clasmatocytes have been demonstrated in patients with streptococcus, pneumococcus, meningococcus, and staphylococcus septicemia, as illustrated in Plate 50 This type of cell is found most frequently in patients with sub acute bacterial endocarditis, in searching for clasmatocytes, blood for smears should be taken from the capillaries of the ear-lobe after gentle massage since this procedure causes an increase in the number and constancy of these cells This type of cell is shown in Plate 51

Monocytosis is a constant finding in certain diseases For instance, the monocytes may be as much as 20 per cent of a leukocytic level of 15,000 per cubic millimeter in infection of the buccal surfaces due to spirillum and fusiform bacillus or Vincent s organisms

Whereas an increased number of monocytes may be found in the

and eccentrically placed nuclei typical of those described for infectious mononucleosis

During ten days of hospitalization the child was afebrile and did not appear ill The lymph nodes continued to diminish in size until they were barely palpable in the cervical region and none were palpable in the axillary or inguinal regions The spleen likewise was not palpable at the time of dis charge One week after entry and three weeks after the onset of the illness the leukocyte level was 10,000 per cubic millimeter, of which 32 per cent were the characteristic large, abnormal lymphoid cells By the twenty fifth day of his illness the leukocyte level had diminished to 6,000 per cubic milli meter and the abnormal mononuclear cells to 20 per cent Review of sec tions of the lymph node removed at biopsy showed changes consistent with those described for infectious mononucleosis

The patient remained in good health after discharge from the hospital and showed no abnormal cells in a peripheral blood smear taken two months after the onset of his illness

Comment In young children, as illustrated by this case, the disease is often acute in onset, associated with high fever, marked lymphadenopathy, and splenomegaly Likewise, the peripheral blood may show so large a number of abnormal mononuclear cells that a malignant condition, such as leukemia, is sometimes suggested The characteristics of these abnormal cells and the absence of associated anemia and thrombocytopenia or of symptoms of bleeding should assist in differentiation If any doubt still exists, biopsy of an enlarged lymph node may give conclusive information

As in this instance, it is not unusual to find that the abnormal lymph nodes persist for two or three weeks or longer Continued leukocytosis and an increase in the percentage of abnormal mononuclear cells for as long as five weeks or more after the onset of the illness is common No symptoms of ill health accompany these changes in the blood

MONOCYTOSIS

In the blood of young children 5 to 10 per cent of the total number of white cells are monocytes Usually, during the process of healing or recovery from an acute infectious disease, an intermediate mono-cytosis may be observed between the early neutrophilic leukocytosis and the late increase in lymphocytes At this time as many as 15 per cent of the cells may be monocytes

Sabin and her co-workers have produced a monocytic reaction experimentally in animals injected with the tubercle bacillus or its

IV. Leukemia

LEUKEMIA, as it has been defined, is an invariably fatal systemic disease primarily involving the blood forming organs and characterized by widespread, rapid, and disorderly prolifera tion of the leukocytes and their precursors and by the presence, almost without exception, at some time during the course of the disease, of immature leukocytes in the blood, often in very large numbers

General Considerations At the present time, the most widely-held opinion is that leukemia is a malignant neoplasm and shares with other neoplastic diseases the mystery as to its cause Strong support for this point of view has been gained from the study of leukemia in man and in laboratory animals, especially mice In this species the disease is comparable in many respects to that seen in man Investigations of leukemia, both in experimental animals and in human beings, have failed to offer proof to support the theory that either an infectious agent or a dysfunction of the glands of internal secretion or an alteration in the metabolism of constituent substances essential for leukocytic proliferation is responsible for its origin

Leukemia is relatively uncommon in children The incidence has been increasing during the past few years, possibly due to the wider recognition particularly of the more obscure leukopenic forms The disease is rare in the neonatal period, although authenticated instances have been reported, in their series of over 200 cases the writers have observed two newborn infants with leukemia The incidence steadily increases after the first year of life The acute forms are more frequent in infants and young children, whereas the chronic forms are as a rule seen only in children over eight years of age

Two members of the same family are seldom afflicted with leukemia, although the disease has been reported in twins and in related individ uals In animal experimentation, intensive in-breeding of cancerous strains has produced offspring which are highly susceptible both to

chronic forms of malaria, in the late manifestations of syphilis, in the early stage of typhoid fever, and occasionally in Hodgkin's disease, their appearance is not of sufficient significance to warrant using this finding as an aid to diagnosis, except possibly in lymphogranulomata

In illustrating the different types of cells seen in leukemia in children, the plates have been arranged as follows

- Stem cell—Plate 52
- Myeloid
  - Acute myeloblastic—Plate 53
  - Acute and subacute myeloid—Plates 54, 55, and 56
  - Chronic myeloid—Plate 57
  - Eosinophilic—Plate 58
- Monocytic—Plates 59 and 60
- Lymphoid
  - Acute lymphoblastic—Plate 61
  - Subacute lymphoid—Plates 62, 63, 64, 67, and 68
  - Chronic lymphoid—Plates 65 and 66

Symptoms The manifestations of leukemia, it has been said, are as protean as those ascribed to syphilis Since leukemic cells, so often blood borne, may invade nearly all organs and tissues, this statement is readily understandable Many of the symptoms are the direct result of the extension of the cells to various regional systems, with consequent enlargement, interference with function, and widespread degeneration of the organs and tissues affected Other symptoms are not clearly explained by so simple a phenomenon as the extension and multiplication of leukemic cells For the sake of clarity, therefore, the symptoms may be separated into (1) the general or non specific manifestations and (2) the special or specific signs of the disease The combination of the general symptoms that may be found in any disease process and the special manifestations dependent upon the infiltration and growth of leukemic cells form the composite picture of leukemia

In the first category and often as the first indication of a malignant process, there may be anorexia, vomiting and vague pain in the abdomen or in other parts of the body Later, as the disease progresses, these symptoms become more severe and occasion much discomfort to the patient Closely associated with them are weakness and fatigue, and when they are accompanied by distressing gastrointestinal symptoms there is loss of weight which may progress terminally to a state of cachexia

the transmitted disease and to the spontaneous appearance of leukemia The common practice of "out-breeding' in the human race may have prevented a similar familial incidence of leukemia

Inasmuch as the etiology is obscure, a classification of the various forms of leukemia entirely satisfactory to the internist, the hematologist, and the pathologist has not yet been devised On the basis of the clinical course and the variations in the types of leukemic cells which appear in the blood, leukemia has been referred to as acute, subacute, or chronic, depending upon the duration of the disease, and as myelogenous, lymphatic, or monocytic, according to the predominating type of cell in the peripheral blood In addition, the terms leukocytic, implying a high level of the immature cells in the circulation, and leukopenic or aleukemic" to denote a low level have been used On the basis of the histo-pathologic changes and the type of invasive cells found in the tissues a variety of terms too great to enumerate in entirety has been introduced, myeloblastoma, reticuloendothelioma, lymphoblastoma, lymphosarcoma, lymphadenosis, leukosis, and myelosis are but a few Although they are not in common use, some of these terms have a logical basis

In children, in contrast to adults, the leukemic cell is often so primitive that, even with the aid of special staining methods, it may be difficult to characterize as either lymphoid or myeloid In the absence of the characteristics that would permit classification, the undifferentiated cells may be called stem" cells and the disease 'stem cell' leukemia Furthermore, the symptomatology, the blood changes, the course, and the prognosis are but little influenced by the dominant type of cell Contrary to the opinion once prevalent, lymphoid leukemia is not much more frequent in the young than myeloid leukemia It is possible that the excessively immature stem cells were mistakenly identified as lymphocytes and that the misconception arose from this error The adjectives leukopenic and leukocytic may be of little value because it is recognized that the number of leukemic cells in the peripheral blood bears no constant relationship to the extent of the disease and that the blood level may undergo alterations to an extreme degree in a short time without significant change in the course of the disease

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Myeloid
 Acute myeloblastic—Plate 53
 Acute and subacute myeloid—Plates 54, 55, and 56
 Chronic myeloid—Plate 57
 Eosinophilic—Plate 58
Monocytic—Plates 59 and 60
Lymphoid
 Acute lymphoblastic—Plate 61
 Subacute lymphoid—Plates 62, 63, 64, 67, and 68
 Chronic lymphoid—Plates 65 and 66

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There is no characteristic temperature reaction. At the onset and for some time thereafter the temperature may be normal or it may follow an insidiously rising curve, until fever is constantly sustained at a level of 103° to 104°F suggesting a septic state. During a remission in the disease, fever may be absent only to recur as a re exacerbation takes place.

Dyspnea and palpitation of the heart, either alone or together and unassociated with profound anemia or localized mediastinal tumor, may develop at almost any stage of leukemia although these are symptoms most commonly present late in the disease.

Local infection of the skin and of the mucous membranes, particularly stomatitis with bleeding and ulceration and swelling of the gums and buccal mucous membranes, may be the first suggestion of a serious underlying disease. Ulceration in the mouth, due to secondary infection, develops most often in patients with a leukopenic *type of leukemia. It is also reported as a regular symptom of the* rare monocytic form.

These general symptoms, while in themselves not suggestive of leukemia, may, when associated with one or more of the special manifestations mentioned below, become significant as indications of the early onset of the leukemic process.

In the second category are the symptoms and signs that arise from the spread and rapid growth of the leukemic cells. Pallor may be noted as the first symptom of the onset of the disease. This and petechiae and ecchymoses with a tendency to free bleeding are unmistakable signs of involvement of the bone marrow and destruction of hematopoietic centers. As the infiltration advances, the anemia becomes more profound and the bleeding tendency more extensive. Intractable hemorrhage from the nose and the mucous membranes of the mouth may occur with or without trauma. The symptoms of bone *marrow invasion are an invariable* accompaniment of leukemia in childhood and, if not present early, always develop in the advanced stages of the disease.

Pain in the bones, sometimes referred to various joints and occasionally shifting from one joint to another, may be associated with tenderness and swelling in such regions. These manifestations are probably due to localized infiltration in the bones and joints, even

though destructive lesions are not always demonstrable by roentgenograms

Metastases to bones may appear throughout the skeletal system A common location is in the region of the orbits, and hemorrhage around the orbits, above or lateral to the eyes, has often been a presenting symptom

A most important sign, occurring in the majority of patients with leukemia, is enlargement of the spleen and often of the liver as well The spleen may be just palpable at the costal margin or it may be so enlarged as to fill completely the abdominal cavity However, in the acute form with a rapidly fatal termination the spleen may not be palpable

Enlargement of the lymph nodes is a variable sign In some instances, enlargement of the cervical lymph nodes is the presenting symptom of the disease, in extreme cases they may reach the size of an egg and on palpation are discrete, non tender, and non-fluctuant More commonly the lymph nodes in the cervical, axillary, and inguinal regions are so slightly involved as to be noted only on careful palpation, but as a rule they increase in size as the disease progresses Variations in the size of the involved lymph nodes is a common occurrence, during a remission the lymph nodes may decrease in size and be barely palpable Enlargement of the mediastinal lymph nodes may be recognized by the onset of a brassy cough, hoarseness, or dyspnea Occasionally, the lymph nodes may become so large as to cause displacement of the mediastinal structures and through interference with the normal flow of blood and lymph bring about the collection of fluid in the pleural and pericardial cavities Involvement of the abdominal lymph nodes, either in the mesentery or the retroperitoneal region, may cause pain which is referred to the um bilicus or to other parts of the trunk Instances have been observed in which, through increasing size of these lymph nodes, obstruction in the gastro intestinal tract or in the bile ducts was produced Like wise, sharply localized pain and tenderness has lead to appendectomy in several patients with leukemia

Since practically any part of the body may be the seat of infiltration with leukemic cells, symptoms indicating involvement of viscera, other than those mentioned above, should not be overlooked

For instance, the kidneys may become enlarged, and metastasizing nodules may appear in the skin and in the scalp

From the above description it is apparent that one regional system may be more extensively involved than another As the disease process advances, the symptoms and signs merge into one another so that often it is not possible at the time of death to determine the site in which the leukemic cells had first localized

Laboratory Data Alteration in the level of leukocytes to a number over 100,000 per cubic millimeter, although not constantly present in leukemia, is a most dependable diagnostic feature, even though in rare instances infection may produce a leukocytosis of this magnitude A high percentage of a single type of 'blast' cell is of paramount importance in diagnosis When the leukocyte level is low (that is, in the leukopenic form of leukemia) the presence of "blast' cells in the peripheral blood should call attention to the possibility of this neo plastic disease However, with a leukopenia the diagnosis may be difficult inasmuch as so few characteristic cells may be found in the blood films

The erythrocytes are generally reduced in number, except early in the course of the acute and subacute forms Anemia may develop so rapidly that the red blood cells may number 1,000,000 per cubic millimeter or less when the patient is first examined The characteristics of the erythrocytes may vary considerably, although usually the red cells are normocytic and normochromic, indicating an aplastic type of anemia resulting from invasion of the bone marrow by the leukemic cells Sometimes a macrocytic cell, well filled with hemoglobin, prevails Reticuloctyes and nucleated erythrocytes, as well as other signs of immaturity of the red-cell series, are present, especially at the onset, and frequently nucleated erythrocytes are so numerous that they overshadow the leukemic cells

The hemoglobin level falls proportionately with the erythrocyte level, except in the macrocytic type of reaction, in which the hemoglobin concentration may be somewhat high for the number of red cells present

An anemia is invariably present in children with leukemia, except at the onset of the most chronic forms

The platelets are lowered constantly to a level below 75,000 per

cubic millimeter, again except at the onset of the chronic forms In infants a secondary thrombocytopenia invariably exists and may show itself by spontaneous bleeding and by the constant prolongation of bleeding time, which may vary from ten minutes to several hours, the retraction of the clot is abnormal, but the coagulation time is normal

Urobilinogen is not present in the urine or in the feces, and the icterus index is within normal limits However, the urine may contain albumen and the sediment occasionally contains large numbers of leukemic cells

Roentgenograms may show diffuse involvement of the long bones and of the skull, particularly in the subacute and chronic forms of leukemia when the leukemic cells localize in or metastasize to the skeletal structures early after the onset In addition, a non specific roentgenographic change in the long bones has been found by us in more than a third of the children with subacute leukemia This consists of a zone of diminished density just proximal to the metaphyseal line in the growing ends of the femur, the tibia and fibula, the humerus, and the radius and ulna Though this has been demonstrated in other conditions, it is suggestive of leukemia, especially in the presence of clinical or hematologic signs of the disease

Diagnosis The greatest difficulty in childhood is the differentiation of acute or chronic infection from malignant neoplasms of the blood Infection, particularly in the young child, commonly produces anemia, thrombocytopenia, and either leukocytosis or leukopenia, with relatively large numbers of immature white cells in the peripheral blood When infection is accompanied by splenomegaly or lymphadenopathy, the picture is often confusing Nevertheless, an unusual leukocytosis with a high percentage of one type of immature cell is suggestive if not pathognomonic of leukemia In the presence of leukopenia, the difficulties of diagnosis from the hematologic data alone are increased as so few typical blast types of cells are to be found For this reason, if any doubt exists, the diagnosis should be made only by histologic examination either of an enlarged lymph node or of bone marrow It is advisable to obtain a block of tissue rather than merely a smear made from puncture of the bone marrow, the spleen, or lymph node, for the structure of the

tissue examined and the relationships of cells may be more important than the presence of immature cells alone In leukemia, the architecture of the lymph node is altered or even obliterated, and the capsule is invaded by large numbers of cells, most of which are immature members of the myeloid or lymphoid series, although in many instances a precise identification is not possible The bone marrow is replaced in large part by similar cells which fill the sinuses and the capillaries Small collections of immature cells of the erythroid series may be present Erythropoietic activity is reduced, often to a marked degree

Aplastic anemia likewise offers difficulties in differentiation from leukemia in the leukopenic stage, since secondary aplasia so often accompanies the neoplastic disease Here again, if, during the course of observation, evidence such as sudden increase in the number or percentage of immature leukocytes in the peripheral blood is not found, histologic examination may be the sole means of confirming the diagnosis

The congenital anemias, such as erythroblastosis fetalis, familial hemolytic anemia, and Mediterranean anemia, frequently resemble leukemia, as they too are characterized by splenomegaly, anemia, and the presence of immature erythrocytes and leukocytes in the peripheral blood Hemolysis and rapid regeneration of erythrocytes in addition to large numbers of immature leukocytes of all types rather than of a single ' blast type should serve to differentiate these anemias from leukemia if the other physical and laboratory evidences are lacking

Infectious mononucleosis, which is often characterized by enlargement of the lymph nodes and splenomegaly in association with a moderate leukocytosis and an increase in the percentage of young mononuclear cell types, may be mistaken for leukemia However, the absence of anemia and thrombocytopenia and the characteristic staining reaction of these abnormal mononuclear cells should serve to distinguish infectious mononucleosis

Lymphosarcoma and lymphoblastoma are so closely related to leukemia that in all instances it is inadvisable to attempt to distinguish between them It is not possible to predict when either one or the other of these neoplastic diseases, apparently limited to a partic-

ular regional system of lymph nodes, may suddenly advance and "blast" cells characteristic of leukemia appear in large numbers in the peripheral blood

Hodgkin's disease, or sclerosing lymphoma, also is closely related to leukemia The early signs and symptoms, such as increasing lymphadenopathy and enlargement of the spleen and the liver, are common to both diseases However, in Hodgkin's disease there is relatively little anemia until late in the course and even then it is of only moderate degree Thrombocytopenia is not constantly present, and the peripheral blood does not show immature forms of leukocytes

Malignant new growths involving the spleen, the liver, or the bone marrow frequently simulate leukemia by clinical signs and symptoms In widespread neuroblastoma in infancy, profound anemia and thrombocytopenia have been demonstrated, but the peripheral blood fails to show any increase in immature leukocytes of a single type, and the changes in the bones and skeletal system shown by roentgenograms tend to be localized rather than diffuse as in leukemia

Agranulocytic angina or neutropenia with angina may offer difficulty in differentiation from the form of leukemia with leukopenia The absence of "blast" type of cells in the peripheral blood after a sufficient period of observation tends to exclude a grave disorder of the blood However, occasionally only biopsy and pathologic examination of the tissue from the bone marrow will give conclusive evidence as to the underlying process producing the anemia and leukopenia

Course and Prognosis The course of leukemia varies considerably, from the most acute form in which the symptoms progress rapidly to a fatal termination within one to four weeks, to the subacute and chronic forms which may continue for months or rarely for a few years It is worthy of note that in these latter forms remissions may occur during which all the signs and symptoms and even the blood changes of leukemia may abate or completely disappear Surprising improvement in the symptoms with a reversal of the hematologic changes sometimes follows recovery from an acute intercurrent infection However, after a few weeks or a few months, the symptoms and signs and hematological evidences of leukemia once more become apparent and the course may rapidly progress to a fatal termination

Treatment Because the disease is invariably fatal, treatment should be directed toward modifying the symptoms so that the patient may enjoy *relative comfort* In the presence of profound anemia and hemorrhage, transfusion of matched whole blood may materially relieve the patient of distressing symptoms for a short time, sometimes this is followed by a remission of longer or shorter duration

Radiation with roentgen rays may be beneficial by making the patient much more comfortable and may even induce a remission Treatment of this kind should be reserved for children with enlargement of the lymph glands or great enlargement of the spleen and liver or with an unusually high leukocytosis It is not advised for the acute forms of leukemia or in the presence of leukopenia with little or no lymphoid or splenic enlargement, as it often produces a more profound anemia and a greater tendency to hemorrhage

Recently radioactive phosphorus, produced in the cyclotron, has been used both orally and parenterally in the treatment of patients with leukemia Because this mineral is deposited in greatest concentration in the bone marrow, the liver, the spleen, and the lymph nodes, it may exercise its greatest benefit in leukemia by virtue of the release of its radioactivity in the very tissues where leukemic cells abound The beneficial effect has been similar to that obtained from radiation by roentgen ray or by exposure to radium or its products, without some of the untoward reactions so frequently resulting from the sudden destruction of tissue which often accompanies large doses of roentgen ray *Although this method of therapy requires further investigation* and experience before it can be accepted without reservation, the benefits so far obtained in making the patient more comfortable, lengthening the periods of remission, and even prolonging life have led to optimism regarding its value, especially in the chronic types of leukemia

Fowler's solution has been used in instances of leukemia with elevated leukocyte levels, occasionally a reduction in the number of circulating immature cells follows but otherwise this has little influence on the course Such a change is usually of short duration, and the medication is not well tolerated because of its tendency to produce nausea and vomiting

Illustrative cases of the different forms of and the variations in leukemia in childhood may clarify the descriptions offered above

CASE RECORD ACUTE LEUKEMIA OF UNDIFFERENTIATED STEM CELL TYPE

A three year old white female child was brought to the hospital because of pallor of three weeks duration and easy bruising of one week s duration The patient had always been in good health until the onset of measles two months before Following this she had appeared weak and tired and the appetite had been poor

Three weeks before entry it was noted that the lips and cheeks were pale in contrast to their previous ruddy color The pallor had been progressive from this time until she was admitted to the hospital One week before entry, without known trauma, several black and blue areas appeared on the lower extremities, and thereafter such areas were frequent on the arms as well as the legs The child s irritability and sleeplessness contrasted with her previous good behavior

Physical examination revealed a very well-developed and well nourished but extremely pale child with numerous petechiae and ecchymoses widely scattered on the face, trunk and extremities The respirations and the pulse rate were rapid There were small but readily palpable lymph nodes in the cervical, axillary, and inguinal regions The spleen was enlarged to the level of the umbilicus and the liver was palpable two finger breadths below the costal margin The heart was enlarged to percussion, and a loud blowing murmur was audible over the apex Petechiae were present on the mucous membranes of the mouth and conjunctivae

Laboratory examination revealed an erythrocyte level of 1,400,000 per cubic millimeter and hemoglobin of 3 9 grams or 25 per cent The leukocytes numbered 120,000 per cubic millimeter, and in the stained smears 95 per cent of these cells were very immature, deeply basophilic cells with scant cytoplasm and dividing nuclei (Plate 52) The platelets numbered 50,000 per cubic millimeter The bleeding time was greatly prolonged

Transfusion was administered in an effort to control the diffuse bleeding phenomena which caused great discomfort to the patient but the effect was only transitory There was no appreciable improvement in the number of erythrocytes or in the amount of hemoglobin in the blood The leukocyte increased to 250 000 per cubic millimeter, with the same high proportion of immature cells Profuse hemorrhage from the nose and mucous membranes, as well as bleeding in the gastro-intestinal tract, developed five days after entry and death occurred eight days after first hospitalization or twenty nine days after the onset of noticeable pallor Necropsy confirmed the diagnosis of widespread leukemia with extensive involvement especially noticeable in the bone marrow throughout the body

Comment This exemplifies the rapid progress of an acute leukemic process, the symptoms of which suggested early bone marrow localization, as

judged by early pallor and petechial hemorrhage The majority of the leukocytes were so immature that differentiation was difficult, the cell therefore being labeled a "stem cell," implying a form earlier than the myeloblast or lymphoblast commonly encountered in other types of leukemia Typical of such rapidly spreading leukemia was the absence of improvement after the transfusion, which produced little or no change in the levels of erythrocytes and hemoglobin Rapidly progressive anemia and thrombocytopenia with widespread hemorrhage produced a fatal outcome in less than one month from the time that first recognizable symptoms of the disease appeared

CASE RECORD ACUTE MYELOBLASTIC LEUKEMIA

A four-year-old white male child was referred to the hospital because of the sudden onset of feverishness, pallor, and uncontrolled bleeding from the nose Previous health had been good There had been an attack of typical chicken pox six weeks before the onset of the present illness

One week before entry the patient suddenly appeared tired and feverish The feverishness continued for the next two days, there was frequent vomiting, and the face as well as the lips became pale Four days before entry the patient appeared somewhat better, except for anorexia and weakness Two days before entry bleeding started from the left nostril and continued off and on for the following forty eight hours despite nasal packing with *epinephrin solution*

Physical examination revealed an acutely ill child breathing rapidly and deeply The pulse rate was 160 per minute, the temperature 103° F The lips, mucous membranes, and skin were very pale There were numerous petechiae and ecchymoses on the skin and mucous membranes as well as on the conjunctivae Bloody nasal crusts filled both nostrils The lymph nodes in the cervical, axillary, and inguinal regions were slightly enlarged The heart was enlarged to percussion and a loud murmur was heard all over the precordium The abdomen was protuberant with enlargement of the spleen and liver, each to two finger-breadths below the costal margin

The laboratory examination revealed an erythrocyte level of 1,200,000 per cubic millimeter and hemoglobin of 4 4 grams or 28 per cent Platelets numbered 22,000 per cubic millimeter and leukocytes 52,000 In the stained smears over 98 per cent of the leukocytes were identified as typical myeloblasts (Plate 53)

The hyperpyrexia continued, with levels between 102° and 105° F Hemorrhage from the nose as well as from the lips and gums was difficult to control The anemia progressed to terminal level of 600,000 erythrocytes per cubic millimeter and two grams of hemoglobin The leukocytes at this time numbered 60,000 per cubic millimeter, and in the stained blood smears the great majority of these were rapidly dividing myeloblasts

Death occurred four days after admission to the hospital

Necropsy confirmed the diagnosis of leukemia localized chiefly in the mar row cavities throughout the body, with moderate involvement of the liver, the spleen, the lymph nodes, and to a lesser extent the kidneys and other organs

Comment This is an example of an acute fulminating type of leukemia evidently localizing early in the bone marrow tissues and producing anemia and thrombocytopenia with bleeding from the mucous membranes The hyperpyrexia which was a notable feature of this child s illness is often seen in the rapidly progressive form of leukemia such as was present in this instance The rapidity of the process was typical of the most acute leuke mias with a total course of less than two weeks from earliest recognizable symptoms The relationship of the acute infection to chicken pox six weeks before the onset of symptoms of leukemia cannot be clearly defined, though such correlation between the acute infectious diseases of infancy and child hood and the leukemic process has been noted before

CASE RECORD CHRONIC MYELOCYTIC LEUKEMIA

A ten year old white female child was brought to the hospital because of fatigue, anorexia, and easy bruising of two months duration Her previous health had been good and her appetite excellent, and a steady gain in weight had been noted until the onset of these complaints In the two months previous to entry there had been gradual loss in weight and diminution in activity because of both fatigue and fear of bruising Physical examination revealed a well developed and well nourished girl with a few ecchymoses on the extremities and over the hips The lips and mucous membranes showed good color There were a few palpable cervical lymph nodes but none else where The heart and lungs were normal The abdomen was slightly pro tuberant The liver was enlarged two finger breadths below the costal margin, and the spleen was easily palpable in the left axillary line three finger breadths below the costal margin

Laboratory examination disclosed an erythrocyte level of 4 500,000 per cubic millimeter and hemoglobin of 14 grams or 90 per cent The platelets numbered 100,000 per cubic millimeter The white count was 120,000 In the stained smears of the blood there were 30 per cent myelocytes of varying degrees of immaturity and 10 per cent myeloblasts

During the ensuing six months there was a gradually developing mild anemia with more pronounced thrombocytopenia and hemorrhagic phenom ena Roentgen ray therapy was given over the mediastinum anteriorly and over the spleen The leukocyte level dropped thereafter to 15 000 per cubic millimeter with a smaller percentage of immature cells During the next sixteen months the patient continued in fairly good health, especially

after two further treatments with deep x ray therapy, given each time the leukocyte count rose above 100,000 per cubic millimeter

Two years after the earliest symptoms had been noted, the patient s erythrocyte count began to drop rapidly, and the leukocytes rose to 200,000 per cubic millimeter with a higher percentage of young myeloid cells The spleen and liver as well as the lymph nodes in the axillary and inguinal regions became still further enlarged Transfusions delayed the progress of the anemia for a few weeks at a time

Twenty six months after the earliest symptoms and two years after first examination, the patient was readmitted to the hospital because of increasing pallor The erythrocyte level had fallen to 1,000,000 per cubic millimeter, the leukocytes numbered 250,000, and the smears showed an increasing proportion of myeloblasts and myelocytes (Plate 57) The platelets at this time were less than 20,000 per cubic millimeter Bleeding from the nose and gums became difficult to control The spleen and liver increased rapidly in size until they almost filled the abdomen Death occurred one week after readmission

Necropsy confirmed a diagnosis of leukemia with extensive infiltration of many organs by myeloblasts and myelocytes

Comment This child suffered from chronic myeloid leukemia of the type more commonly seen in adults Such long duration is rarely seen in younger children *There was marked improvement after deep roentgen ray therapy,* administered over the heart and great vessels to affect the largest amount of circulating blood cells However, after three series of such treatment there was less improvement and a more rapid progress in the disease as evidenced by widespread enlargement of lymph nodes and increasing splenomegaly and hepatomegaly, with diminution in erythrocyte and platelet levels Death occurred twenty-six months after the first symptoms had been noted

CASE RECORD SUBACUTE MONOCYTIC LEUKEMIA

A nine-year-old white female child was brought to the hospital because of fatigue and anorexia of two months duration Her previous health had been good, her appetite had been excellent, and activities had been normal for her age

Two months before entry the patient s appetite began to diminish and continued to be progressively poorer with subsequent loss in weight At the same time the child s activities were noticeably curtailed and she complained of tiredness and weakness after slight exertion

Physical examination revealed a well developed and well nourished child with moderate loss of subcutaneous fat The lips and mucous membranes were somewhat pale and there were occasional petechiae on the neck and

lower extremities The cervical lymph nodes were enlarged but not tender The mouth showed a few ulcers of the shallow, non inflamed type in the buccal mucous membrane opposing the upper and lower molars The heart was slightly enlarged and there was a hemic murmur heard over the apex Abdominal palpation disclosed the spleen at the level of the umbilicus reaching the mid clavicular line and the liver three finger breadths below the costal margin extending into the right upper quadrant

Laboratory examination revealed an erythrocyte level of 3,500,000 per cubic millimeter and hemoglobin of 10 grams or 64 per cent The platelets numbered 75,000 per cubic millimeter The leukocyte count was 30,000 per cubic millimeter and 60 per cent of the cells in the stained smears were large mononuclear forms, classified as young and rapidly dividing monocytes (Plate 60)

During the following two months the lymph nodes gradually enlarged in size and became tender The spleen and the liver likewise became larger The anemia progressed slowly and the leukocyte level rose from 30 000 to 60,000 per cubic millimeter with an increasing percentage of young mononuclear cells classified as monoblasts and young monocytes Terminally there were 95 per cent of such cells and less than three per cent mature polymorphonuclear neutrophils in the peripheral blood smears

The ulcerated areas on the buccal mucous membranes increased in size and number and were refractory to treatment with antiseptic solutions Six weeks after hospital admission and one week before termination of the disease, these ulcerations became confluent and a large sloughing lesion was present on the buccal mucous membranes extending onto the soft palate There was membrane formation over this lesion with organisms underneath the membrane typical of the Vincent s spirochetes and bacilli This local oral infection continued to extend until the palate tonsillar fossae, and pharynx became greatly edematous and deglutition and respiration were embarrassed In the last week of the illness the temperature increased, with fluctuations between 103 and 105° F

At necropsy the diagnosis of leukemia with wide spreading infiltration of monocytic cells was confirmed Recent secondary infection of a terminal type involving the upper and lower respiratory tracts was present

Comment The leukemia in this patient was of the subacute type with cells in the peripheral blood identified as of monocytic origin The ulcerative stomatitis with terminal infection and noma like appearance is described as more common in monocytic leukemia than in any other variety When there is a marked deficiency in polymorphonuclear neutrophils such anginal symptoms may be found in other types of leukemia as well

CASE RECORD ACUTE LYMPHOBLASTIC LEUKEMIA

A two-year-old white male infant was brought to the hospital because of abdominal pain, high fever, and increasing pallor of four days' duration The previous health had been excellent and the child had grown and developed far beyond the average for his age

Four days before entry abdominal pain accompanied by vomiting and high fever had appeared suddenly This pain was generalized and apparently intense and cramplike It had suggested an acute inflammation in the abdominal cavity but there were no physical signs to confirm this The pain had diminished slightly in the following three days but it was noted that there was increasing pallor

Physical examination revealed an acutely ill infant with marked pallor of the skin and mucous membranes There was slight enlargement of the lymph nodes in the cervical, axillary, and inguinal regions and the spleen and the liver were slightly enlarged to palpation The heart rate was rapid and a hemic murmur could be heard all over the precordium

Laboratory examination showed an erythrocyte count of 1,700,000 per cubic millimeter The leukocytes were 100,000, and in the stained smears 98 per cent of these cells were moderate-sized lymphoblasts with scant basophilic cytoplasm and nucleoli in the nucleus (Plate 61)

In the ensuing five days the temperature ranged between 102° and 105° F, the patient complained constantly of abdominal pain, and bleeding from the nose and mouth recurred frequently Terminally the erythrocytes numbered less than 1,000,000 per cubic millimeter and the leucocyte level remained above 100,000, all the white cells being typical lymphoblasts

Necropsy confirmed the presence of a widespread leukemic process Although the spleen and liver, the bone marrow, the kidneys, and other organs were sites of localization of the leukemic cells, the most unusual abnormality was the great enlargement of the lymph nodes in the mesentery of the intestines and the tremendous engorgement of the Peyer s patches in the small intestines

Comment This case typifies an acute type of lymphoblastic leukemia in which the total duration from the sudden onset of symptoms was less than ten days The complaint of severe and recurrent abdominal pain may have been related to the great swelling and enlargement of the mesenteric lymph nodes demonstrated at necropsy Although this may have been the site of earliest localization of the leukemic cells, the process had spread to involve many organs and tissues throughout the body

CASE RECORD ARTHRALGIC OR RHEUMATOID TYPE OF LEUKEMIA WITH LEUKOPENIA

A boy, six and a half years old, was brought to the hospital because of fever, pain in the joints, and limitation of activity which had persisted for nine months The family history and the past history were unessential

The present illness began nine months before entry with the complaint of pain in the right ankle for one week there had been difficulty in walking Feverishness was noted at this time Seven months before entry his left ankle became tender and painful on motion, and this attack again was accompanied by fever Three months before entry both ankles were tender to touch, and movement was extremely painful Feverishness and epistaxis accompanied this recurrence of the symptoms Two months before entry there was pain in the back which interfered with activity and the patient was put to bed for a short period Two weeks before entry feverishness was again noted for three days and there was tenderness and swelling in the right wrist In the intervals between attacks, the patient seemed entirely well, was up and about, was afebrile, and exhibited normal activity Because of these symptoms, the diagnosis of rheumatic fever seemed entirely justified

The physical examination revealed a pale, undernourished boy with tender, swollen ankle joints and severe pain in the lower spine associated with spasm and kyphosis There was no enlargement of the lymph nodes or of the spleen

The erythrocytes numbered 2 500,000 per cubic millimeter, and the hemoglobin was 7 5 grams or 48 per cent The leukocytes numbered 3,500 per cubic millimeter of which 12 per cent were immature blast types There were 65 000 platelets per cubic millimeter

The patient s temperature fluctuated between 101 and 103 F during the first week of hospitalization and pain and swelling were present in both ankle joints and in the right wrist The number of leukocytes fell to 500 per cubic millimeter, of which 80 per cent were immature cells Roentgenograms revealed generalized osteoporosis with compression fracture of the first and second lumbar vertebrae

During the following six months there was an intermittent fever of irregular type and migrating swelling and tenderness of various joints The lymph nodes and the spleen gradually became enlarged to palpation and the anemia steadily increased The leukopenia persisted with levels of between 500 and 2,500 cells per cubic millimeter, the majority of these being immature blast forms probably of the lymphoid type (Plate 64)

Fifteen months after the onset of his first symptoms and six months after first hospitalization the patient died Post mortem examination confirmed the diagnosis of leukemia

CASE RECORD ACUTE LYMPHOBLASTIC LEUKEMIA

A two-year old white male infant was brought to the hospital because of abdominal pain, high fever, and increasing pallor of four days duration The previous health had been excellent and the child had grown and developed far beyond the average for his age

Four days before entry abdominal pain accompanied by vomiting and high fever had appeared suddenly This pain was generalized and apparently intense and cramplike It had suggested an acute inflammation in the abdominal cavity but there were no physical signs to confirm this The pain had diminished slightly in the following three days but it was noted that there was increasing pallor

Physical examination revealed an acutely ill infant with marked pallor of the skin and mucous membranes There was slight enlargement of the lymph nodes in the cervical, axillary, and inguinal regions and the spleen and the liver were slightly enlarged to palpation The heart rate was rapid and a hemic murmur could be heard all over the precordium

Laboratory examination showed an erythrocyte count of 1,700,000 per cubic millimeter The leukocytes were 100,000, and in the stained smears 98 per cent of these cells were moderate-sized lymphoblasts with scant basophilic cytoplasm and nucleoli in the nucleus (Plate 61)

In the ensuing five days the temperature ranged between 102° and 105 F , the patient complained constantly of abdominal pain, and bleeding from the nose and mouth recurred frequently Terminally the erythrocytes numbered less than 1,000,000 per cubic millimeter and the leucocyte level remained above 100,000, all the white cells being typical lymphoblasts

Necropsy confirmed the presence of a widespread leukemic process Although the spleen and liver, the bone marrow, the kidneys, and other organs were sites of localization of the leukemic cells, the most unusual abnormality was the great enlargement of the lymph nodes in the mesentery of the intestines and the tremendous engorgement of the Peyer s patches in the small intestines

Comment This case typifies an acute type of lymphoblastic leukemia in which the total duration from the sudden onset of symptoms was less than ten days The complaint of severe and recurrent abdominal pain may have been related to the great swelling and enlargement of the mesenteric lymph nodes demonstrated at necropsy Although this may have been the site of earliest localization of the leukemic cells, the process had spread to involve many organs and tissues throughout the body

small lymph nodes palpable in the left cervical and mandibular regions The pain subsided, and the patient seemed entirely well, although the paralysis of the face persisted Five weeks later the leukocytes in the peripheral blood increased suddenly to over 100 000 per cubic millimeter Stained smears revealed 90 per cent of these cells as immature lymphoid in type similar to those described at the examination on entry (Plate 68) The erythrocytes at this time numbered 4 000 000 per cubic millimeter, and the hemoglobin was 10 grams or 64 per cent The platelets were reduced to 60,000 per cubic millimeter

Within three days of this sudden elevation in leukocyte level, there was widespread lymphadenopathy and palpable enlargement of the spleen and the liver The anemia and thrombocytopenia progressed so that ten days after this sudden change the erythrocytes numbered 1,500,000 per cubic millimeter and the platelets 25,000 Enlargement of the mediastinal lymph nodes produced troublesome cough and dyspnea with marked engorgement of the jugular vessels Symptoms of pneumonia appeared twelve days after the sudden elevation in leukocytes, and the patient succumbed two days later

Necropsy confirmed the presence of widespread leukemic infiltration

Comment At entry this patient appeared to be suffering from a localized neoplasm involving the lymph nodes of the cervical region with no evidence of involvement of the spleen, the liver or the bone marrow Blood examination, however, revealed some immature lymphoid cells in the peripheral circulation These disappeared soon after entry Biopsy confirmed the presence of a malignant neoplasm in the cervical lymph nodes The patient appeared well for more than three weeks, but then facial palsy developed that indicated infiltration about the facial nerve About two months after first entry, there was evidence of widespread leukemic infiltration throughout the body, and a rapidly down hill course followed The total duration of the process from the earliest symptoms was almost three months This illustrates the close relationship between the localized tumors of lymph nodes and the widespread disease ordinarily classified as leukemia

CASE RECORD CHRONIC LYMPHOID LEUKEMIA

An eight year old boy was referred to the hospital because of enlargement of the cervical lymph nodes of one month s duration His health had been good until two months before entry when he complained of a slight sore throat and was feverish for three days He seemed entirely recovered from this when one month before entry there was slight enlargement of the cervical lymph nodes below the angle of the jaw on each side, unassociated with feverishness or sore throat Local application of heat and of ice failed to give any relief and the patient was allowed to continue his normal activi

Comment This case is typical of the leukemia with leukopenia which manifests arthralgic symptoms and pursues a subacute to chronic course A diagnosis of rheumatic fever was entertained when the patient was first seen but subsequent tests—revealing decreasing numbers of leukocytes with an increasing percentage of immature cells, together with thrombocytopenia and a relatively profound anemia—pointed to leukemia of the leukopenic stage rather than to rheumatoid arthritis The evidence of these tests was strengthened by roentgenograms showing extreme osteoporosis (a condition that eventually led to the development of a compression fracture in the lumbar vertebrae) The termination was typical of leukemia, with the increase in the size of the spleen and the lymph nodes, the progressive anemia, and the presence of large numbers of immature blast forms in the blood smears

CASE RECORD SUBACUTE LYMPHOBLASTIC LEUKEMIA, LOCALIZED LYMPHOBLASTOMA TERMINATING IN LEUKEMIA

A five year old white female child was brought to the hospital because of swelling of the lymph nodes in the cervical region of two weeks' duration The patient had been in good health previously and had had no recent infection Two weeks before entry the lymph nodes immediately below the angles of the jaw became visibly enlarged, but there was no pain or feverishness or other systemic symptom of illness In the following week this lymphadenopathy progressed until more than half a dozen nodes could be palpated on each side

Physical examination revealed a well-developed and well nourished child without pallor or petechiae Except for enlargement of the lymph nodes in the cervical region, no abnormalities were noted Roentgenograms showed no noticeable change in the heart, lungs, mediastinum, or abdominal organs

Laboratory examination disclosed an erythrocyte level of 4,800,000 per cubic millimeter with hemoglobin of 12 6 grams or 81 per cent The platelets numbered 240,000 per cubic millimeter and the leukocytes 8,000, of which 20 per cent were immature lymphoid cells (Plate 67)

During a week of observation the patient was comfortable and afebrile, but there was no change in the enlarged lymph nodes in the neck The blood remained unaltered, except for the disappearance of the immature lymphoid cells from the peripheral blood as judged by repeated inspection of the stained smears Biopsy of an enlarged lymph node was performed Examination was reported as showing changes consistent with lymphoblastoma

The child remained comfortable and symptom free during the ensuing two weeks Twenty-four days after entering the hospital, the patient suddenly complained of excruciating pain in the left side of her face and developed a left facial palsy Examination at this time revealed several new

Necropsy confirmed the diagnosis of widespread lymphoid leukemia

Comment The course of the leukemic process in this case was typical of the chronic form of lymphoid leukemia as seen in childhood The total duration from the earliest symptoms of lymphadenopathy was eight and a half months At first entry the leukemic process appeared to involve chiefly the lymph nodes of the cervical region and to a lesser extent the spleen and the liver and other regional systems of lymph nodes There was excellent response to deep roentgen ray therapy on two separate occasions at four month intervals When recurrence occurred eight months after the first onset of symptoms there was further evidence of widespread infiltration of the bone marrow as judged by profound anemia and thrombocytopenia Another trial of roentgen ray treatment was ineffective in shrinking the lymphoid tissue, and a fatal termination occurred soon after the second admission to the hospital Failure to respond to this previously effective mode of therapy is frequently seen in the course of leukemia of the chronic or subacute type

ties until one week before entry when the lymphadenopathy had increased sufficiently to cause further discomfort

Physical examination revealed a well developed and well nourished child without pallor, petechiae, or ecchymoses of the skin The cervical lymph nodes were enlarged, non tender, and so numerous as to fill the neck and supra-clavicular spaces There was moderate enlargement of the axillary and inguinal nodes as well An occasional harsh cough and increased dullness about the sternum suggested mediastinal lymph node enlargement The abdomen was prominent because the spleen reached to the umbilicus and the liver filled the right upper quadrant

Examination of the blood showed an erythrocyte count of 4,500,000 and hemoglobin of 12 grams or 77 per cent The platelets numbered 150,000 per cubic millimeter The leukocyte count was 30,000 and in the stained smears of the blood 35 per cent of the cells were classified as lymphoblasts

The patient was afebrile throughout the first three weeks of hospitalization Biopsy of an axillary lymph node revealed infiltration of the tissues by immature lymphoid cells Deep roentgen ray therapy was given with prompt shrinkage in the cervical and mediastinal lymph nodes and some diminution in the size of the liver and the spleen The patient was sufficiently improved to be discharged one month after first admission to the hospital He continued relatively symptom free for the following four months, after which recurrence of lymph node enlargement was noted The leukocyte level at this time was 12,000 per cubic millimeter with 20 per cent lymphoblasts appearing in the peripheral blood smears The erythrocytes and the hemoglobin were at low normal levels A week after the recurrence of lymphadenopathy there was further growth in these structures and another course of deep roentgen ray therapy was administered Once again improvement occurred which lasted for almost two months

Eight months after the first onset of symptoms the patient was re-admitted because of cough and increasing dyspnea At this time there was also moderate pallor of the skin and mucous membrane and petechiae about the neck, face, and extremities A moderate degree of lymph node enlargement was present in the cervical, axillary, and inguinal regions The spleen and the liver were enlarged almost to the iliac crest There was evidence of enlarged mediastinal lymph nodes both by physical examination and by roentgenograms The erythrocyte level at this time was 1,800,000 per cubic millimeter and the hemoglobin measured 5 5 grams or 35 per cent The platelets numbered only 70,000 per cubic millimeter The leukocyte count was 80,000 per cubic millimeter, 75 per cent of the cells in the stained blood smears were classified as lymphoblasts (Plate 65) Transfusion and further deep roentgen ray therapy produced relatively little improvement in the symptoms and signs of the disease and, following a rapid downward course, death occurred two weeks after the second admission to the hospital

When symptoms of free bleeding, such as petechiae and ecchymoses and a tendency to oozing or prolonged bleeding with little or no trauma, are present in association with a low platelet level, the disease is called thrombocytopenic purpura This is in differentiation from similar symptoms that may occur without any alteration from normal in the platelet level, this condition is known as purpura simplex or symptomatic purpura

It should be emphasized again that primary thrombocytopenic purpura is diagnosed as such only by exclusion of all the known underlying causes for the platelet deficiency With increasing skill and further investigation, the diagnosis of primary purpura becomes less common The description offered below for primary purpura fits the secondary forms equally well except for symptoms and signs due to the underlying cause

PRIMARY THROMBOCYTOPENIC PURPURA

This disease is characterized by a bleeding tendency associated with lowered levels of platelets in the circulating blood The bleeding time is prolonged, the clotting time is normal, and retraction of the clot is delayed or fails to develop Synonyms are purpura hemorrhagica, cryptogenic purpura, and Werlhoff s disease

General Considerations Primary thrombocytopenic purpura rarely occurs in more than one member of a family At times there is a history of recent infection, but little reliance can be placed on this as the chief causative factor for the platelet disturbance Females are affected more frequently than males and young children more often than older children A predisposition to allergic manifestations, especially asthma, has been noted in some patients

Many theories have been advanced to explain the pathogenesis of this disease Some writers believe that a toxic effect on the mega karyocytes in the bone marrow inhibits adequate formation and extrusion of blood platelets The platelets then produced are not only few in number but are larger in size than normal platelets Alterations from normal in the appearance and staining of the megakaryocytes in the bone marrow support this view

Other investigators have suggested that the spleen has an inhibitory

V. The Platelets

The blood platelets, or thrombocytes, constitute one of the three cellular elements of the circulating blood The site of origin of the platelets is not definitely proved, but the theory generally accepted is that they arise from the megakaryocytes or giant cells in the bone marrow

A decrease in the number of blood platelets below the normal level is referred to as thrombocytopenia or thrombopenia A reduction in the number below a critical level tends to cause prolongation in the bleeding time and delay or failure in clot retraction With this there is usually associated a hemorrhagic tendency leading to the appearance, with or without trauma, of hemorrhages in the skin, in the subcutaneous tissues, from the nose and mouth, and in nearly all regional systems

An increase in the number of blood platelets above the normal level is known as thrombocytosis and a marked and persistent increase is termed thrombocythemia This state is conducive to the development of thrombotic manifestations

THROMBOCYTOPENIA

Thrombocytopenia may occur without any noticeable symptoms of free bleeding or even prolongation of bleeding time Occasionally a platelet level of 75,000 per cubic millimeter or less is discovered incidentally while determining the red or white cell counts Such a low level may exist for years with no associated petechiae, ecchymoses, or bleeding tendency

Thrombocytopenia may be separated into the primary and secondary forms The latter is by far more common It is often due to infection, either current or recent Toxins, malignancies, especially leukemia, allergic states, and aplasia of the bone marrow may all induce thrombocytopenia When no known cause for the lowered platelet level is discovered it is termed primary thrombocytopenia

with ecchymoses of all sizes there and on the trunk as well Occasionally, epistaxis of moderate severity may be the first sign of the bleeding tendency Since the hemorrhage is seldom extensive, pallor is not usual Physical examination reveals no abnormality other than the widespread sites of bleeding and occasionally a slightly enlarged spleen on palpation After a varying length of time the purpuric manifestations may disappear and a complete remission may occur

The third type, a chronic recurrent form, has attracted the most attention There are periodic episodes of hemorrhage of greater or less severity with intervals of apparently perfect health when, although the platelets remain at about the same low level, the bleeding tendency lessens These fluctuations may continue for many years without appreciable change When bleeding has been checked by transfusion, immediate recurrence is less likely even though the platelets remain low Such crises of purpura may be initiated by infection but often occur without any ascertainable cause The type of bleeding varies Some patients have frequent crops of petechiae on the skin as well as in the mouth The buccal mucous membrane and the tongue may become tender and painful on this account Profuse hemorrhage from mucous or serous membranes, from the nose, uterus, kidneys, or intestines, with or without petechiae, may occur Cerebral hemorrhage may result from relatively mild trauma but fortunately this is rare Aside from the bleeding and its consequences, this type of purpura has no peculiar symptoms More extensive hemorrhages produce pallor and anemia The common accompaniments of such an anemia are prostration, cardiac palpitation and distress, headache, dizziness, and vomiting Profound, even fatal, collapse may result from prolonged and continued loss of blood The spleen may or may not be palpable, though it generally is slightly enlarged Although a spontaneous remission may take place, even after several years, the chronic course of the disease and the severity of the recurring hemorrhages may be indications for specific surgical interference

Laboratory Data The blood shows decrease in platelets, with the level (estimated in 3 per cent sodium citrate solution) usually below 75,000 per cubic millimeter (the normal level is 200,000 to 400,000) Occasionally the number may be as low as 20,000 to 30,000 per cubic

influence on the formation of platelets Kaznelson believed that in this disease the platelets are destroyed in the spleen in excessive numbers and more rapidly than normal The occurence of splenomegaly in many cases of primary purpura has lent support to the possible etiologic relationship between overactivity of this organ and the appearance of purpura In pursuance of this idea, splenectomy seems a logical method of curing the disease

Many observers contend that in addition to the lowered platelet level there is an increased permeability of the blood capillaries which permits escape of blood through the walls of small blood vessels In many instances this can be demonstrated by the so-called positive tourniquet or capillary resistance test (Rumpel-Leede phenomenon), which leads to the appearance of petechiae after partial stasis in the veins of the arm

Symptoms and Signs Primary thrombocytopenic purpura may be separated somewhat arbitrarily into three types according to the symptoms and duration of the disease

The first and most serious, though fortunately the rarest form, is fulminating purpura hemorrhagica in which the first attack may prove fatal despite treatment Here the tendency to bleed appears suddenly in a patient who has been perfectly well Petechial hemorrhage and ecchymoses in the skin and mucous membranes are widespread Bleeding from the nose, the mouth, the genito urinary tract, and the gastro-intestinal tract may be extensive and difficult to control Even the central nervous system may be the site of widespread petechial hemorrhage In addition to the visible locations of gross bleeding, the patient may have hidden hemorrhage, and pallor may develop rapidly Hemorrhages in the mouth may interfere with ingestion of fluids or food, and secondary infection of the mucous membranes at these oral hemorrhages is prone to occur Abdominal pain may accompany the gastro-intestinal bleeding Other signs and symptoms are dependent on the site and the amount of blood lost Hemorrhage in the lungs with terminal pneumonia is an ever-present danger

The second and most common form runs a more benign course of between three and eighteen months The earliest complaint is the increasing frequency of bruising, particularly on the extremities,

In distinguishing between primary and secondary thrombocytopenic purpura, it is important to note that in the primary form the only alterations in the blood are the platelet deficiency and the secondary anemia which may result from blood loss Any other variation, such as leukopenia or marked leukocytosis, or profound anemia unrelated to hemorrhage, or the appearance of immature or abnormal leukocytes, indicates another possible cause for the thrombocytopenia, which therefore would be of the secondary type The greatest difficulty is encountered in differentiation from leukopenic leukemia in infants and children, for in this age group thrombocytopenic purpura, which is almost invariably present, may be the first indication of leukemia

Aplastic anemia of either the primary or the secondary type is likewise associated with lowered thrombocyte levels and purpuric manifestations, but the erythrocyte and leukocyte levels are also greatly depressed and this should serve as the important differential point

If an accurate diagnosis cannot be reached by the correlation of the clinical and hematologic data, histologic examination of the bone marrow is indicated Infiltration with leukemic cells may then establish association of the thrombocytopenic purpura with a malig nant process replacement of normal hematopoietic foci with either fat or fibrous tissue would indicate aplastic anemia as the underlying factor

Spontaneous recurrent nosebleeds, with or without a tendency to ecchymoses on the extremities following slight trauma, are common in familial telangiectasis In this condition, however, there is no alteration in the platelet level, and local examination may reveal the dilated capillaries which are characteristic of the disease

Symptomatic purpura with spontaneous bleeding, as well as petechial and post traumatic hemorrhage, is a frequent accompaniment of or sequel to infection When such hemorrhage involves the gastro intestinal tract with abdominal pain as a prominent feature, the name Schönlein s purpura has been applied Likewise, hemorrhage about the joints, with petechial manifestations, has in the past been termed Henoch s purpura Since these terms merely connote the localization of a bleeding process and have neither etiologic nor

millimeter The stained blood smear reveals the absence of platelets in clumps as they are normally seen, and only occasional large, less-well-stained thrombocytes are found during the examination of many high-power fields (See Plate 69)

The bleeding time, as determined from a needle-puncture wound in the finger or the lobe of the ear, is usually prolonged to twenty minutes or more, and sometimes pressure on the bleeding point is required to control the continual oozing Occasionally, even when the platelet level is low, the bleeding time may be normal, but usually such a finding is transitory The coagulation time is normal but a delay in or failure of clot retraction is characteristic of this disease

The erythrocytes show no abnormality other than that which may result from loss of blood Prolonged or oft-repeated hemorrhage leads to the appearance of hypochromic microcytic red cells typical of the secondary anemia that develops An increase in the percentage of reticulocytes, as well as a leukocytosis with a relative increase in the number of polymorphonuclear neutrophils, likewise follows acute blood loss

Diagnosis Primary thrombocytopenic purpura is easily distinguished from other bleeding states by a low platelet level, prolonged bleeding time, and delay in or failure of clot retraction, together with the presence of petechiae and ecchymoses widely scattered over the body and the mucous membranes, and the tendency to spontaneous hemorrhage from the nose, mouth, or gastro-intestinal tract Although the estimation of the bleeding time is valuable, the presence of a normal bleeding time as occasionally seen is not necessarily inconsistent with the diagnosis of purpura hemorrhagica Hemophilia can be excluded by the familial incidence and its occurrence in the male only, by the normal platelet level, the prolonged clotting time, and normal retraction of the clot

The differentiation of primary purpura from the secondary type, which is far more common, should be the first and most important consideration in diagnosis Determination of the underlying cause of the secondary type may offer immediate indication for therapy Infection, either localized or generalized, is of the greatest etiologic significance, for recovery from the infection is generally followed by return of the platelet level to normal with a complete remission of the purpuric manifestations

these, large amounts of calcium medicinally or in the diet are indicated Radiation by x ray has been applied over the long bones Liver and liver extract, both by mouth and intramuscularly, have been given in large amounts All the therapeutic measures mentioned above have been tried by us but without uniform success

Splenectomy has been widely recommended However, the operative mortality tends to be high in the acute form of purpura In the chronic form, the results are fairly satisfactory but not so brilliant as was first expected by Kaznelson in 1916 Within two weeks after removal of the spleen the majority of patients have an increase in platelets which persists and thereafter they remain symptom free But a few patients have merely a transitory rise in platelets with a subsequent fall to the former level, and some show practically no rise in platelet level after operation Even so they may be benefited, for recurrences of bleeding are less frequent and less severe It should be reiterated that splenectomy should be reserved for patients with chronic thrombocytopenia, as many children grow out of their bleeding tendency and therefore do not require surgical interference

CASE RECORD PRIMARY THROMBOCYTOPENIC PURPURA

An eleven year old girl was admitted because of recurring attacks of epistaxis over a period of five years There was no history of prolonged bleeding or easy bruising in any other member of the family

The present illness had begun with a nosebleed at the age of six years Up to the time of entry there had been at least one attack of epistaxis a week, usually lasting ten to fifteen minutes, not associated with trauma or respiratory infection For a few months these episodes occurred almost every day Four months before entry there had been complete relief from this complaint for a period of fifteen weeks Two weeks before entry she had begun to have profuse hemorrhages from the nose controlled only by packing and cauterization of bleeding points on the mucous membrane From the onset of her illness there had been ecchymoses following the slightest trauma

The physical examination revealed a well developed and well nourished girl with numerous ecchymoses and purpuric spots over the body The spleen was palpable at the costal margin There were no other abnormalities

Laboratory examinations showed an erythrocyte level of 4,700 000 per cubic millimeter, a hemoglobin of 12 5 grams (80 per cent), and a leukocyte

therapeutic significance, they are no longer in common usage Symptomatic purpura is not associated with diminution in the platelet level and this fact is important in differential diagnosis

Course and Prognosis In acute fulminating purpura hemorrhagica the extensiveness of hemorrhage, as well as the rapidity of blood loss, merits a grave outlook Despite replacement of blood by transfusion, the hemorrhage may quickly get beyond control and the course of the disease may be very short Secondary infection may occur early Interference with the proper ingestion of fluid and food and recurrent vomiting and diarrhea may hasten the fatal termination

In the milder form, with its relatively short course of a few months, spontaneous remission with little or no tendency to relapse is the rule and a favorable prognosis may be given

The chronic form with its duration of two years or more may show alternating periods of extensive petechiae and gross hemorrhage even though the platelets remain constantly at a low level Exsanguinating uterine hemorrhages often develop with the onset of the menstrual cycle The normal replacement of the deciduous by the permanent teeth may be accompanied by prolonged slow bleeding Surgery even of a minor nature may be dangerous The frequent recurrence of serious bleeding over a long period of time indicates the need for a guarded prognosis

Treatment Treatment should be directed to the control of the bleeding, to the promotion of rapid regeneration of erythrocytes, and to the prevention of further hemorrhage The only effective method for checking an extensive hemorrhage is transfusion with whole blood Several transfusions may be necessary before the bleeding can be controlled and a remission induced

For bleeding that is prolonged or recurrent but not dangerously severe, many therapeutic measures have been advised Coagulant preparations such as thromboplastin, snake venom, placental coagulant, and rabbit globulin, may be beneficial when applied locally to superficial hemorrhage Moccasin venom has been given subcutaneously in gradually increasing amounts and decreasing dilutions to improve capillary resistance Parathyroid extract has been injected intramuscularly for the purpose of inducing hypercalcemia, and tachysterol has been administered orally for the same purpose With

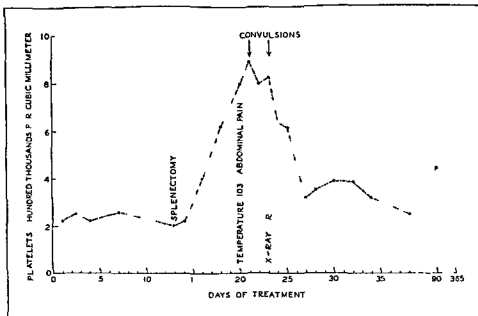


CHART 19 Thrombocytosis, platelet crisis following splenectomy in congenital hemolytic anemia This may occur in any disease for which splenectomy is performed especially when the initial platelet level is normal Note the evidences of intra abdominal thromboses in the severe pain and sudden temperature elevation followed by intracranial thromboses with convulsions Spontaneous fall in the platelets may occur but x ray treatment and intravenous injection of heparin or other anticoagulants may control symptoms and hasten remission of the platelet crisis

THROMBOCYTOSIS AND THROMBOCYTHEMIA

Thrombocytosis has been observed in many conditions, such as injuries and burns, post operatively in many surgical conditions, following hemorrhages, and in acute hemolytic anemias (see Chart 19) The increase in platelets in such cases is always a transitory condition, their level usually returns to normal as soon as bodily repair has taken place, ordinarily after one or two weeks

The term thrombocythemia has been used to indicate a persistent increase in the platelets which may occur after splenectomy (see Plate 70) except in cases of purpura hemorrhagica and aplastic anemia and in some instances of polycythemia, which in childhood is always secondary to anoxemia associated with chronic heart disease

level of 8,500 The platelets numbered between 40,000 and 70,000 per cubic millimeter on repeated counts The bleeding time varied from nineteen minutes on entry to three minutes after prolonged bed rest The clotting time was three minutes and the clot retraction was poor The tourniquet test was positive

During her hospitalization the patient showed no hyperpyrexia or evidence of acute or chronic disease There were frequent, profuse nosebleeds requiring nasal packing and cauterization of the bleeding points

In the following year numerous forms of therapy were tried in an attempt to produce an increase in the platelets No improvement was noted

At the age of twelve years, in addition to her frequent epistaxes, the patient began having profuse menstrual bleeding every two months, lasting six to fifteen days Transfusion was required after each of these uterine hemorrhages Because of the development of this serious disturbance, which did not respond to endocrine therapy, splenectomy was performed when the patient was thirteen years old The spleen was moderately enlarged, weighing 175 grams, and on section showed moderate fibrosis and congestion Slight evidence of hematopoiesis and hemosiderosis was noted The histologic picture was not pathognomonic of any particular disease

Following operation the patient s platelets rose from 36,000 to 180,000 per cubic millimeter on the fifth day, to 260,000 on the fifteenth day, and then fell to 140,000 on the twenty first day, they remained between 150,000 and 200,000 per cubic millimeter throughout the ensuing fifteen months The menstrual periods became regular and short and scant Bleeding from the nose and the appearance of ecchymoses have not recurred

Comment This patient had suffered from epistaxis for over five years but not of sufficient degree for her to seek medical advice so that it is impossible to estimate how long the thrombocytopenic state may have been present before admission to the hospital After the diagnosis was established various forms of medical treatment were tried without demonstrable effect

When at the age of twelve years profuse menstrual bleeding began, with extreme loss of blood necessitating transfusion after each such period, surgical intervention was indicated Following splenectomy, the patient s platelets rose rapidly and the hemorrhagic tendency disappeared There was no further excessive hemorrhage during the menstrual periods and no bleeding from the nose or into the skin after trauma

Such surgical interference is warranted when life is endangered by the long duration or frequency of hemorrhages or after the condition has failed to improve over an extended period Splenectomy without a trial period of symptomatic treatment is usually not advisable because so large a percentage of children recover spontaneously

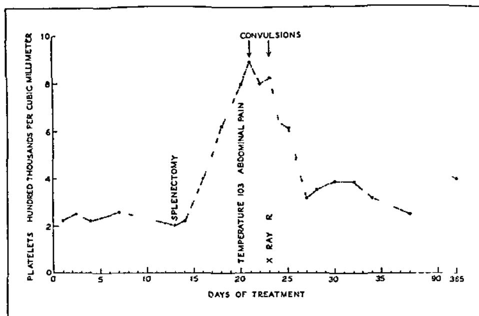


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The cause of thrombocythemia is not clear Two theoretical possibilities exist (1) increased formation of blood platelets due to overactivity of the megakaryocytes in the bone marrow, and (2) diminished destruction of the blood platelets by the reticulo-endothelial system, especially after splenectomy There is evidence to support both of these theories, since the bone marrow in many instances shows increase in the number and size of the megakaryocytes and since splenectomy is so frequently followed by an elevation in the platelet level

The relationship of the platelet levels to splenomegaly and thrombosis both before and after splenectomy has been investigated recently by Rosenthal and his associates As pointed out by them, an elevated platelet level in association with splenomegaly may increase even further very rapidly after splenectomy and may persist as a dangerous thrombocythemia In such instances recurrent thromboses, particularly in the portal system and the mesenteric veins, are common For this reason, splenectomy should not be advised too lightly for patients with normal or high platelet levels and the dangers of thrombotic episodes after splenectomy should be kept in mind The following case record illustrates this type of disease

CASE RECORD THROMBOCYTHEMIA

A girl five and a half years old was brought to the hospital because of severe abdominal pain of twelve hours duration associated with fever and vomiting

In her past history the details of importance were that there had been an attack of hematemesis at the age of two years for which hospitalization and transfusion were necessary Splenectomy had been performed shortly after improvement from this illness In the intervening three years the patient had appeared well, except for occasional attacks of abdominal pain associated with fever and vomiting, lasting twenty-four to forty eight hours These required no medical attention

Twelve hours before entry the child complained of severe pain in the right lower quadrant radiating to the upper abdomen This was cramplike in character and interfered with sleep and activity Feverishness developed a few hours after the onset of this complaint, and the child vomited clear fluid repeatedly

Physical examination revealed an acutely ill child, complaining of pain

constantly The temperature was 104° F, and the pulse rate 160 per minute The face was pale but the lips and mucous membranes were normal in color There was rapid, somewhat labored respiration Abdominal examination showed spasticity of the muscles and generalized tenderness to pressure, especially in the mid abdomen Examination of the blood disclosed an erythrocyte level of 4,800,000 per cubic millimeter, and hemoglobin of 14 grams or 90 per cent The leukocytes numbered 35,000 per cubic millimeter, of which 85 per cent were polymorphonuclear neutrophils The platelets numbered 950,000 In the smear there were numerous large clumps of platelets, as well as an increase in single forms

Within twenty four hours the temperature, the vomiting, and the abdominal pain had entirely subsided, the leukocyte level had fallen to 12 000 per cubic millimeter, and the platelets numbered only 450,000 per cubic millimeter The patient appeared entirely well on the fourth day after entry and remained so until the tenth day, at which time the platelets had risen to 1,200,000 per cubic millimeter On the eleventh day, pain recurred and was again associated with fever and vomiting and signs of an acute abdomen Two days after the recurrence of these symptoms the platelets had fallen to 600,000 per cubic millimeter, and the patient seemed entirely well again

In the following four years the patient had several similar attacks of abdominal pain At the onset of each attack the platelet level was about 1,000,000 per cubic millimeter or higher Following attacks the platelets numbered about 500,000 per cubic millimeter

Comment This child suffered from obstruction in the portal or splenic circulation with subsequent hematemesis Splenectomy was performed with apparent improvement for several years However after the operation the platelets increased to more than 1 000 000 per cubic millimeter On several occasions, the child complained of abdominal pain and exhibited symptoms usually associated with an acute abdomen Following each attack the platelet level diminished rapidly and the patient recovered It was assumed that the abdominal pain with fever, spasticity of the abdominal muscles, and vomiting were associated with extension of thromboses in the mesenteric vessels This phenomenon has been related to the portal obstruction from which the patient originally suffered as well as the thrombocythemia which developed and was constantly maintained after splenectomy Following each episode of extension of thrombosis, the platelet level diminished rapidly As the number of platelets increased again, the danger of recurrence became greater

It is important to differentiate the signs and symptoms of such thrombotic episodes from those usually associated with an acute inflammation of the

intestines or of the peritoneum The history of previous spleno-portal obstruction and especially of splenectomy followed by a marked increase in the number of platelets in the peripheral blood should suggest thrombosis in the mesenteric vessels and serve as a contra-indication to exploratory laparotomy

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ERRATA IN THE PLATES

PLATE 2 nos 16–19
Read *Eosinophilic* for *Esoinophilic*

PLATE 3 nos 1 3
Read *neutrophilic* for *neutrophlic*

PLATE 3 nos 13 14
Read *disrupted* for *dirsupted*

PLATE 4 last line
Read *periphery* for *perhiphery*

PLATE 6 last line
Read *neutrophils* for *neutrohpils*

PLATE 12 no 1
Read *reticulocytes* for *rectiulocytes*

PLATE 27 first line of paragraph
Read *in* for *is*

PLATE 28 second line of caption
Read *Anemia* for *Amenia*

PLATE 35 no 1
Read *o erlving* for *o erlaying*

PLATE 43 no 1
Read *lymphocyte* for *lympocyte*

LIST OF PLATES

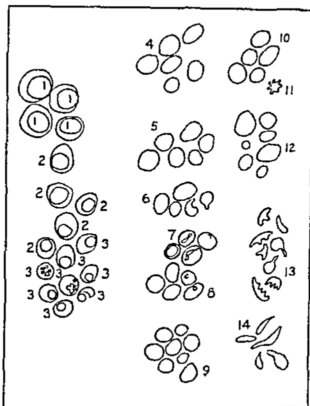
32 Congenital hemolytic anemia during crisis
33 Sickle cell anemia
34 Sickle cell anemia
35 Neutrophils shift to the left in acute infection
36 Neutrophils toxic granulation in prolonged infection
37 Neutrophils acute bacteremia
38 Neutrophils acute toxemia caused by extensive severe burn toxic granulation
39 Eosinophils allergy
40 Eosinophils chronic infection
41 Lymphocytes chronic iron deficiency anemia
42 Lymphocytes pertussis
43 Lymphocytes severe pertussis
44 Lymphocytes infectious mononucleosis
45 Lymphocytes infectious mononucleosis
46 Lymphocytes infectious mononucleosis
47 Monocytes acute primary tuberculosis
48 Monocytes acute primary tuberculosis
49 Monocytes lipoid histiocytosis or Pick-Niemann s disease
50 Monocytes active phagocytosis in chronic bacteremia
51 Monocytes extreme phagocytosis in bacterial endocarditis
52 Acute stem cell or undifferentiated cell type leukemia
53 Acute myeloblastic leukemia
54 Acute myeloid leukemia
55 Acute myeloid leukemia
56 Subacute myeloid leukemia
57 Chronic myeloid leukemia terminal stage
58 Chronic eosinophilic leukemia
59 Acute monocytic leukemia
60 Subacute monocytic leukemia
61 Acute lymphoblastic leukemia
62 Subacute lymphoid leukemia
63 Subacute lymphoid leukemia leukopenic stage
64 Subacute lymphoid leukemia leukopenic stage
65 Chronic lymphoid leukemia
66 Chronic lymphoid leukemia plasma cell type
67 Early subacute lymphoid leukemia, leukopenic stage
68 Subacute lymphoid leukemia terminal leukocytosis
69 Chronic thrombocytopenia purpura hemorrhagica
70 Thrombocytosis following splenectomy

LIST OF PLATES

32 Congenital hemolytic anemia during crisis
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70 Thrombocytosis following splenectomy

KEY TO PLATE I

Maturation in Erythrocyte Series



1—*Megaloblasts* Nucleus is broken up in appearance and dark purple in staining reaction Cytoplasm is deeply basophilic, irregular in staining with clear zones of lighter color toward the center

2—*Erythroblasts* Nucleus is more condensed but still broken up in appearance and darkly staining with coarser clumps of chromatin Cytoplasm is less basophilic, though varying amounts of bluish color are still present at the periphery, definite reddish hemoglobin color is apparent through the basophilia

3—*Normoblasts* Nucleus is dense and pyknotic, in many instances fragmented and occasionally partly extruded Cytoplasm is the usual reddish color of hemoglobin, the basophilia having almost completely disappeared

4—*Polychromatophilic erythrocytes* or *polychromatocytes* Young erythrocytes still retaining some of the basophilic staining reaction, with the reddish hemoglobin background, a multicolored appearance results and therefor the name

5—*Punctuate basophilic stippling* with black to bluish granules in the cells This is usually seen in severe anemia and in toxic disturbances

6—*Hypochromic erythrocytes* The concentration of hemoglobin is deficient usually indicating iron lack or interference with hemoglobin synthesis Cells often have only a ring of hemoglobin at the periphery and usually are small

7—*Cabot rings* Remnants of nuclear membrane appearing as circles or figures of eight in the cells

8—*Howell Jolly bodies* Nuclear remains of varying size staining dark blue or black

9—*Reticulocytes* Young forms of erythrocytes, staining characteristically with a vital dye such as cresyl blue before counterstaining with Wright s The reticulum a fine network of blue or purple threads, may be concentrated in the center of the cell or spread out diffusely, occasionally it will appear almost punctuate in character

10—*Normal mature erythrocytes* or *normocytes* Cells are about 7 micra in diameter and contain enough hemoglobin to give the whole cell a pinkish red stain except at the biconcave center where very little stain is evident

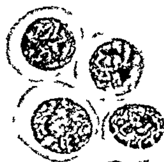
11—*Pyknotic erythrocyte* An artifact often produced by faulty fixation or staining of blood films

12—*Macrocytes* and *microcytes* Cells larger and smaller than normal

13—*Poikilocytes* Cells of abnormal shape, most commonly tailed forms

14—*Sickle cells* Cells pulled out of normal shape into sickled form This trait is found almost exclusively in Negro blood it is best produced by depriving susceptible fresh cells of oxygen or exposing them to carbon dioxide

PLATE I



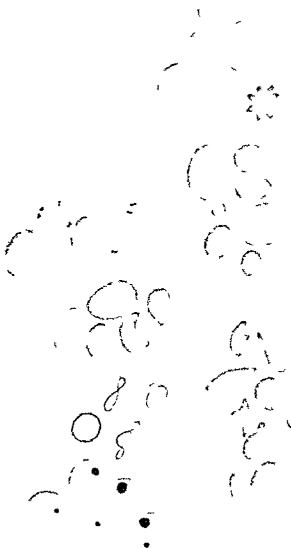


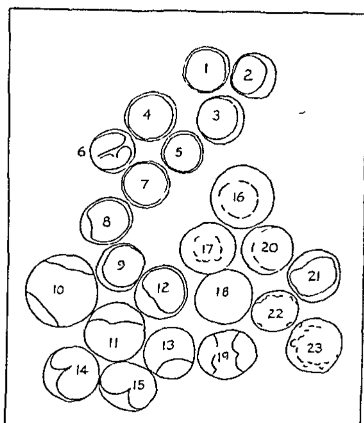












KEY TO PLATE 2

Maturation in Myeloid Series

1–6—*Myeloblasts* Nucleus is large with one or more nucleoli an occasional nucleus is in process of division Cytoplasm is scant and intensely basophilic

7 8—*Myelocytes type A*, or *premyelocytes* Nucleus is more condensed Cytoplasm has beginning non specific dark granulation often edging over the nucleus

9–13—*Myelocytes type B*, showing increasing maturity Nucleus is smoother more condensed with no nucleoli Cytoplasm is more abundant with less basophilia, granulation is still dark and non specific often partly covering the nucleus

14, 15—*Myelocytes type C*, *metamyelocytes* or *late myelocytes* Nucleus is often indented Cytoplasm is fairly light blue in staining dark, coarse granulation being replaced by fine neutrophilic granulation

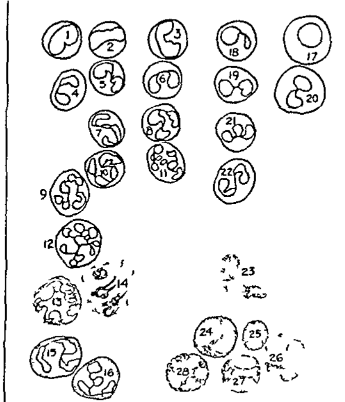
16–19—*Eosinophilic myelocytes* Cytoplasm contains large granules of eosinophilic type filling the cell and often covering and obscuring the nucleus which is generally round and light staining

20–23—*Basophilic myelocytes* Nucleus is undifferentiated light staining Cytoplasm is filled with large, heavy dark blue to black granules often partly covering the nucleus

PLATE 2



x1500



KEY TO PLATE 3

Maturation in Myeloid Series—(*continued*)

1–3—*Young neutrophils* also called *early band form,* or *non segmented neutro phils* Nucleus is condensed and beginning to lobulate Cytoplasm contains full complement of neutrophilic granules

4–6—*Adult neutrophils* Nucleus has two lobes Cytoplasm is packed with granules

7, 8—*Adult neutrophils* Nucleus has three lobes

9 10—*Adult neutrophils* Nucleus has four or more lobes

11 12—*Aging neutrophils* Nucleus has multiple lobulation Cytoplasm contains sparser granules and some vacuoles

13 14—*Degenerated neutrophils artifacts* Old and fragile cells disrupted in smear ing process

15 16—*Adult neutrophils* Cytoplasm contains larger but fewer granules which stain heavily—so called toxic granules—and some vacuoles This type of cell is *common in severe infections and intoxications*

17—*Young eosinophil* Nucleus is not lobulated as yet Cytoplasm is packed with large eosinophilic granules

18–21—*Adult eosinophils* Nucleus usually has two or three lobes Cytoplasm is filled with typical granules

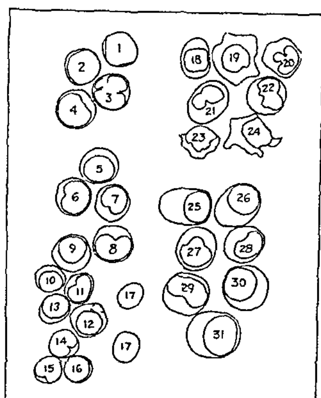
22—*Aging eosinophil* Vacuolization in cytoplasm is beginning

23—*Aging eosinophil* Old and fragile cell disrupted in smearing process

24–26—*Basophils* Nucleus usually has two or three lobes Cytoplasm is gen erally filled with very large blue black granules

PLATE 3





KEY TO PLATE 4

Maturation in Lymphoid Series

1–4—*Lymphoblasts* Nucleus *is large, containing one or more nucleoli, an occasional* nucleus is in process of division, as in 3 Cytoplasm is scant and basophilic

5–7—*Large* or *young lymphocytes* Nucleus is somewhat condensed with tendency to spoke like arrangement of chromatin Cytoplasm *is fairly* clear blue

8, 9—*Large lymphocytes* Nucleus is condensed Cytoplasm is fairly abundant and is clear light blue containing several to many large reddish granules toward periphery of cell

10–12—*Medium lymphocytes* Nucleus is condensed Cytoplasm is moderate in amount, occasionally containing reddish granules

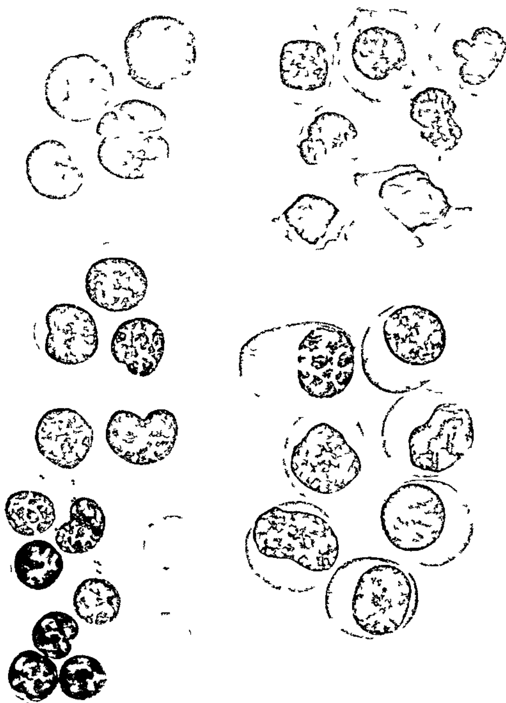
13–16—*Small* or *adult lymphocytes* Nucleus is condensed Cytoplasm is scanty and clear blue

17—*Erythrocytes,* for comparison of size

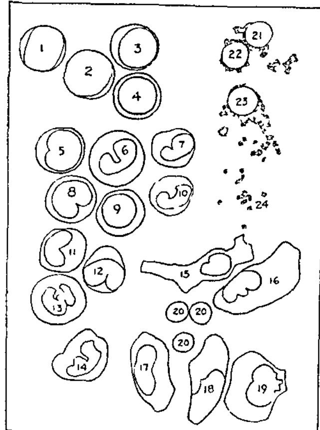
18–24—*Large lymphocytes* of the type seen most frequently in infectious mononucleosis Nucleus is dense with some fenestration of chromatin and is often eccentrically placed Cytoplasm is abundant with irregular edge which molds itself around adjacent cells it is clear light blue denser at margin and may contain some reddish granules

25–31—*Lymphocytes* of plasma cell type Nucleus is eccentrically placed darkly staining with dense chromatic clumps often in cart wheel arrangement Cytoplasm is abundant dark blue with clear areas near nucleus and stains more densely at perhiphery it often has foamy appearance

PLATE 4



x1500



KEY TO PLATE 5

Maturation in Monocyte and Thrombocyte Series

1–4—*Monoblasts*: large cells with relatively small amount of cytoplasm showing moderate basophilia. Nucleus is large and loose in structure, but stains fairly evenly; one or more nucleoli.

5–14—*Monocytes*: Nucleus has fine chromatin network, and is often horseshoe or kidney shaped. Cytoplasm is abundant and stains a light grey blue; it contains fine reddish blue granules, mostly toward periphery; occasionally granules are darker and more abundant, as in 7, 9 and 10; often there is a clear zone in the cytoplasm at the "hof" or indentation of the nucleus. Occasionally there are vacuoles, evidence of active phagocytosis, at the periphery of the cytoplasm as in 14.

15–19—*Mononuclear phagocytes*, *endothelial phagocytes* or *clasmatocytes*: the largest cells ordinarily found in the peripheral blood. Nucleus is eccentrically placed. Cytoplasm is finely granulated and contains many vacuoles of all sizes, often filled with ingested material; it stains light blue.

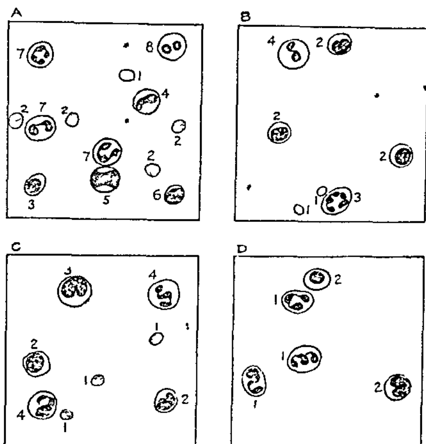
20—*Erythrocytes*, for comparison of size.

21–23—*Megakaryocytes*: These cells are very rarely found in the peripheral blood. Nucleus is dense, often of jelly like, homogenous appearance. Cytoplasm is light blue with dark purple masses of granules and no visible cellular membrane; it often trails in long pseudopods, as in 23, and masses of platelets break off and are scattered as individual platelets.

24—*Platelets* or *thrombocytes*.

PLATE 5





KEY TO PLATE 6

Normal Blood at Different Ages

Section A Age 3 days Definite macrocytosis and hyperchromia and immaturity of the erythrocytes are shown also a relative increase in myeloid cells with young forms predominating

1—Macrocyte	5—Myelocyte
2—Reticulocytes	6—Small lymphocyte
3—Erythroblast	7—Adult neutrophils
4—Band form of neutrophil	8—Eosinophil

Section B Age 3 months There is relative microcytosis and hypochromia with few reticulocytes also relative lymphocytosis

1—Hypochromic microcytes	3—Adult neutrophil
2—Lymphocytes	4—Eosinophil

Section C Age 2 years Slight hypochromia is often still evident Reticulocytes are slightly more numerous Lymphocytes and neutrophils are almost equal in number

1—Reticulocytes	3—Monocyte
2—Lymphocytes	4—Neutrophils

Section D Age 6 years Normal adult type of blood picture is now present with normocytic normochromic erythrocytes and increase of neutrophils over lymphocytes

1—Neutrohpils	2—Lymphocytes

PLATE 6

A



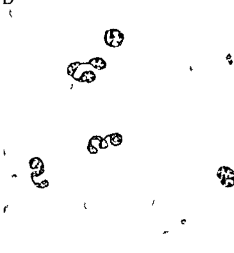
B



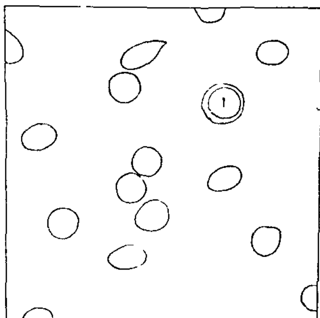
C



D



x600



KEY TO PLATE 7

Aplastic Anemia

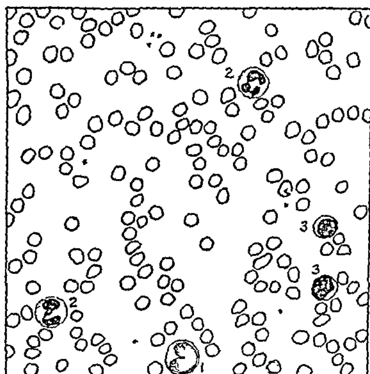
The erythrocytes are normal in size and hemoglobin content but decreased in number absence of reticulocytes and of polychromatophilic cells is evidence of lack of erythropoiesis Leukocytes are few in number and predominantly of the lymphocytic type, and platelets are absent

1—Small lymphocyte

PLATE 7



x1500



KEY TO PLATE 8

Chronic Hypoplastic Anemia

Erythrocytes appear to be normal in size and hemoglobin content but are reduced in number. Reticulocytes are greatly reduced, none being present in the field shown. Platelets are not quite as numerous as normally. Leukocytes are somewhat reduced with relatively greater reduction in neutrophils.

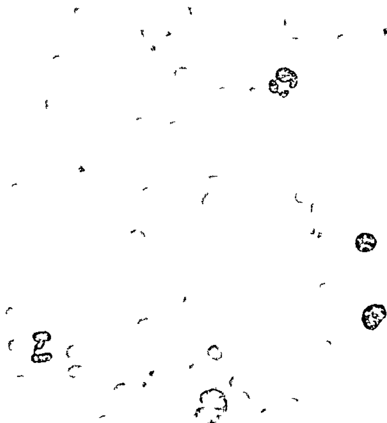
This blood picture differs from that of aplastic anemia only in degree, especially in the counts of platelets and leukocytes.

1—Monocyte

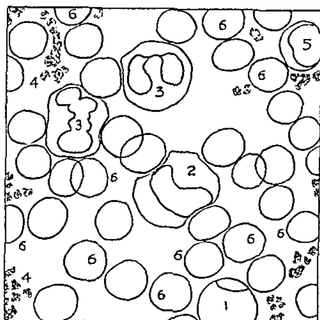
2—Neutrophils

3—Lymphocytes

PLATE 8



x600



KEY TO PLATE 9

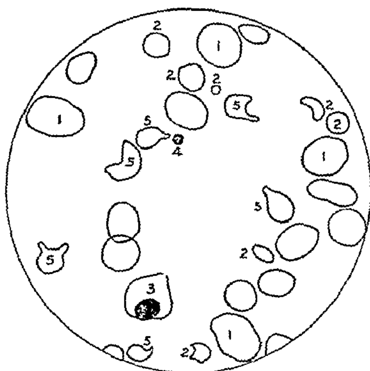
Normocytic Normochromic Anemia
due to Acute Hemorrhage

Evidence of great bone marrow activity is seen in the *marked increase in reticulocytes, in leukocytes (especially myeloid cells) and in platelets In contrast to the picture in* chronic hemorrhage (Plate 18) the erythrocytes are normal in size and in hemoglobin content

1—Myelocyte
2—Band form of neutrophil
3—Neutrophils
4—Masses of platelets
5—Medium lymphocyte
6—Reticulocytes

PLATE 9





KEY TO PLATE 10

Macrocytic Hyperchromic Anemia
due to Intestinal Anomaly Early Stage

The erythrocytes are often of the large type oval shaped and well filled with hemoglobin Some cells are very small others are abnormally shaped There are occasional nucleated red cells *Often reticulocytes are absent as in this field*

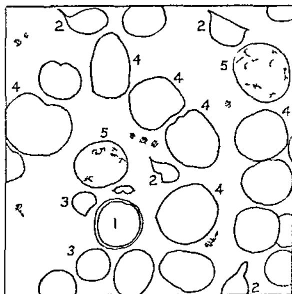
This condition is comparable to primary Addisonian anemia (pernicious anemia) in adults

1—Macrocytes
2—Microcytes of various sizes and shapes
3—*Normoblast*
4—Platelet
5—Poikilocytes

PLATE 10



x1500



KEY TO PLATE II

Macrocytic Hyperchromic Anemia following Infection and Complete Achlorhydria Before Treatment

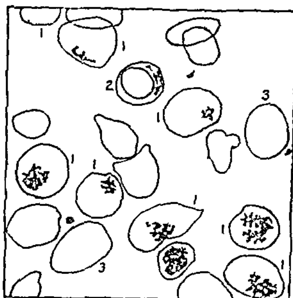
Most erythrocytes are enormous but there are occasional small abnormally shaped forms There are few reticulocytes Leukocytes are reduced with lymphocytes predominating

1—Small lymphocyte
2—Poikilocytes
3—Microcytes
4—Macrocytes
5—Reticulocytes

PLATE II



x1500



KEY TO PLATE 12

Macrocytic Hyperchromic Anemia
Sixth Day after Injection of Liver Extract

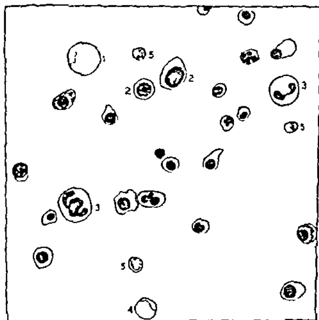
Cells are still macrocytic but increased erythrogenesis is evidenced in presence of reticulocytes and occasional nucleated red cells

1—Rectiulocytes
2—Erythroblast
3—Macrocytes

PLATE 12



x1500



KEY TO PLATE 13

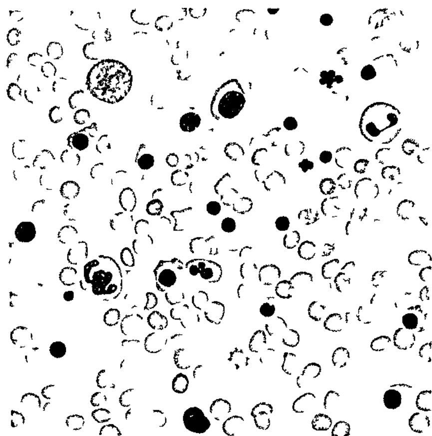
Erythroblastosis Fetalis or Hemolytic Anemia of the Newborn

Erythrocytes are predominantly macrocytic, and there are many nucleated forms. Reticulocytes are greatly increased, even for this age (two days) The leukocytes are increased in number and are often of immature types Platelets are scarce or absent

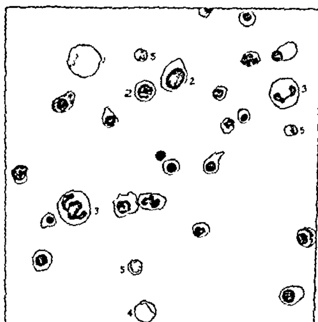
1—Myelocyte
2—Erythroblasts
3—Polymorphonuclear neutrophils
4—Small lymphocyte
5—Reticulocytes

All unmarked nucleated cells are normoblasts

PLATE 13



x600



KEY TO PLATE 13

Erythroblastosis Fetalis *or*
Hemolytic *Anemia of the* Newborn

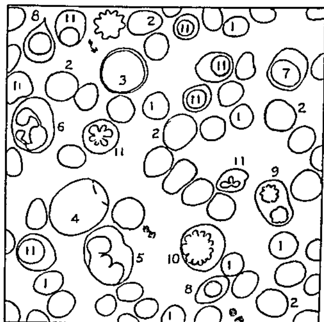
Erythrocytes are predominantly macrocytic and there are many *nucleated forms* Reticulocytes are greatly increased even for *this age* (two days) The leukocytes are increased in number and are often of immature types Platelets are scarce or absent

1—*Myelocyte*
2—*Erythroblasts*
3—Polymorphonuclear *neutrophils*
4—Small lymphocyte
5—Reticulocytes

All unmarked *nucleated* cells are normoblasts

PLATE 14





KEY TO PLATE 14

Erythroblastosis Fetalis or
Hemolytic Anemia of the Newborn
Severe Form

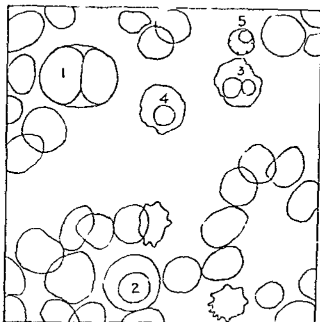
Striking features in this field are the macrocytosis and the large number of nucleated erythrocytes in every stage of maturation Reticulocytes also are numerous The amount of cresyl blue used in this film was insufficient to stain all the reticulum and therefore some polychromatophilia is seen Leukocytes are increased in number and tend to be immature Platelets are scarce

1—Reticulocytes
2—Macrocytes
3—Myeloblast
4—Myelocyte type B or early myelocyte
5—Monocyte
6—Polymorphonuclear neutrophil
7—Medium lymphocyte
8—Erythroblasts
9—Erythroblast with double nucleus
10—Erythroblast with fragmented nucleus
11—Normoblasts

PLATE 15



x1500



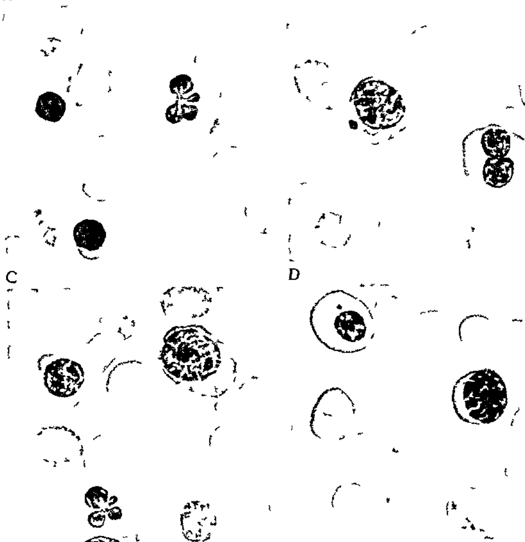
KEY TO PLATE 15

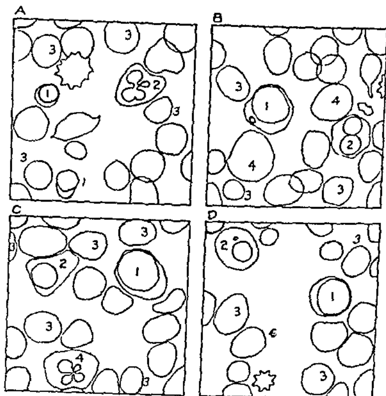
Erythroblastosis Fetalis or Hemolytic Anemia of the Newborn

Greater magnification showing some of the varieties of nucleated erythrocytes

1—Dividing megaloblast with intensely basophilic cytoplasm
2—Late erythroblast, nucleus is becoming condensed and cytoplasm shows only slight residual basophilia
3—Normoblast with fragmentation of nucleus
4—Normoblast large size
5—Normoblast with basophilic stippling in cytoplasm

PLATE 16





KEY TO PLATE 16

Erythroblastosis Fetalis or Hemolytic Anemia of the Newborn

Selected fields showing further details of typical macrocytosis and erythroblastosis

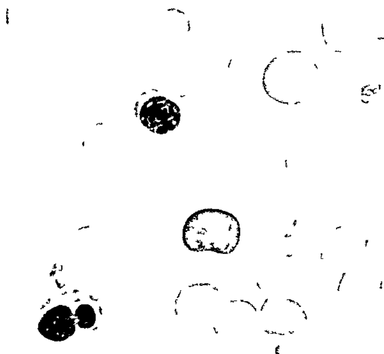
A 1—Small normoblasts
2—Large normoblast with fragmenting nucleus
3—Reticulocytes

B 1—*Erythroblast* Nucleus is not condensed nuclear fragments are broken off cytoplasm is basophilic
2—Normoblast with fragmenting nucleus
3—Reticulocytes
4—Macrocytes

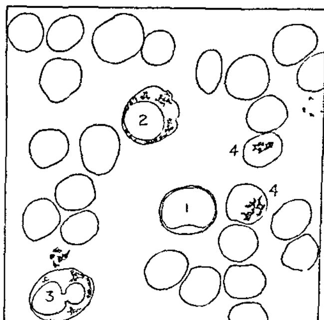
C 1—Large early erythroblast Nucleus shows chromatin clumps, cyto plasm is intensely basophilic and only a small amount of hemoglobin pigment is visible
2—Large erythrobla t
3—Reticulocytes
4—Normoblast with fragmenting nucleus

D 1—Erythroblast
2—Normoblast containing Howell Jolly body in addition to the nucleus
3—Reticulocytes

PLATE 17



x1500



KEY TO PLATE 17

Erythroblastosis Fetalis or
Hemolytic Anemia of the Newborn
Mild Form

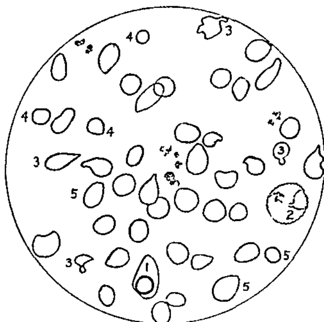
The number of macrocytes and reticulocytes is unusually large for the age There are only occasional nucleated erythrocytes

1—Medium lymphocyte
2—Normoblast with reticulum in cytoplasm
3—Normoblast with reticulum in cytoplasm
and fragmenting nucleus
4—Reticulocytes

PLATE 18



x1200



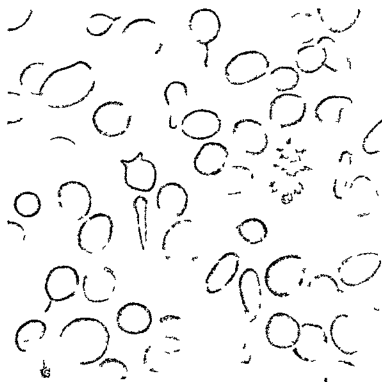
KEY TO PLATE 18

Microcytic Hypochromic Anemia due to Chronic Blood Loss

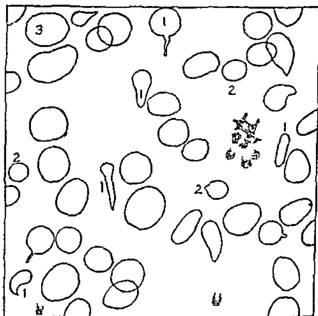
Erythrocytes are predominantly microcytic, some have only rings of hemoglobin stained red at the periphery of the cell Polychromatophilic cells are frequent Leukocytes are relatively scarce with lymphoid cells predominating Platelets are normal

1—Medium lymphocyte
2—Eosinophil
3—Hypochromic poikilocytes
4—Hypochromic microcytes
5—Polychromatophilic cells

PLATE 19



x1500



KEY TO PLATE 19

Microcytic Hypochromic Anemia

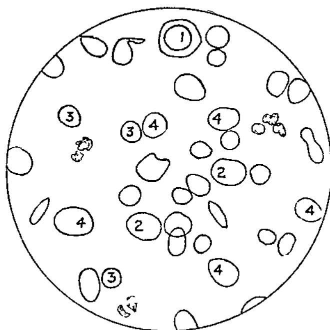
The erythrocytes tend to be smaller than normal and are markedly deficient in pigment, there are occasional poly chromatophilic cells and some poikilocytes Leukocytes are reduced in number, none appear in this field Platelets are normal

1—Poikilocytes
2—Hypochromic microcytes
3—Polychromatophilic cell

PLATE 19



x1500



KEY TO PLATE 20

Microcytic Hypochromic Anemia
Shortly after Treatment with Iron

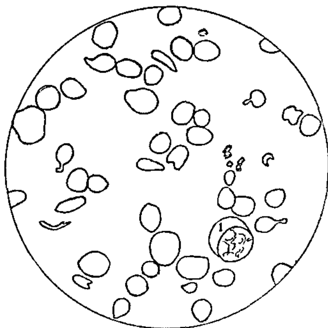
Erythrocytes are chiefly microcytic and hypochromic but a few normocytic normochromic cells are now evident Occasional nucleated erythrocytes are seen and polychromatophilic cells are increasing in number

1—Normoblast
2—*Polychromatophilic cells*
3—Hypochromic microcytes
4—Normocytic normochromic cells

PLATE 20



x1500



KEY TO PLATE 21

Microcytic Hypochromic Anemia
due to Iron Deficiency and Secondary Infection

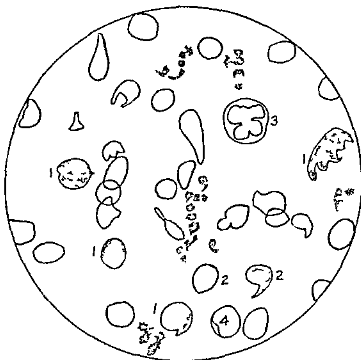
Marked hypochromia and microcytosis anisocytosis and poikilocytosis great distortion of red cells

1—Medium lymphocyte

PLATE 21



x1500



KEY TO PLATE 22

Microcytic Hypochromic Anemia due to Iron Deficiency and Prolonged Infection

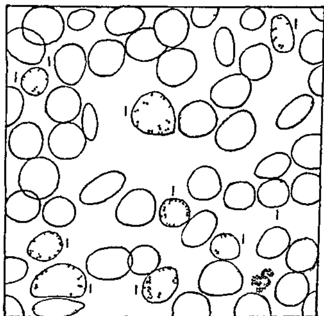
There is extreme variation in size and shape as well as hemoglobin content of the erythrocytes Some regeneration is evidenced by the appearance of reticulocytes and nucleated erythrocytes Many stippled red cells are present

1—Reticulocytes
2—Stippled cells
3—Normoblast
4—Small lymphocyte

PLATE 22



x1200



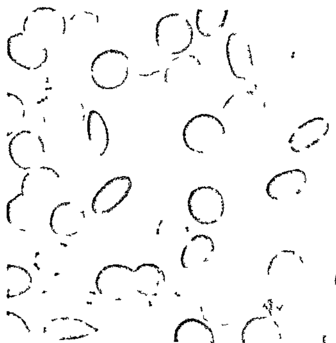
KEY TO PLATE 23

Microcytic Hypochromic Anemia due to Severe Lead Poisoning

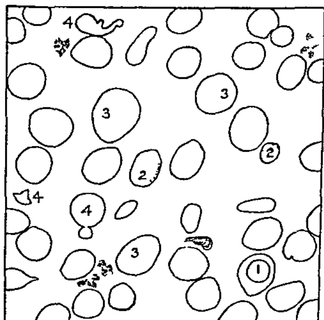
Cells are moderately small and are deficient in hemoglobin There is basophilic stippling in a large percentage of them particularly the polychromatophilic cells

1—Stippled cells

PLATE 23



x1500



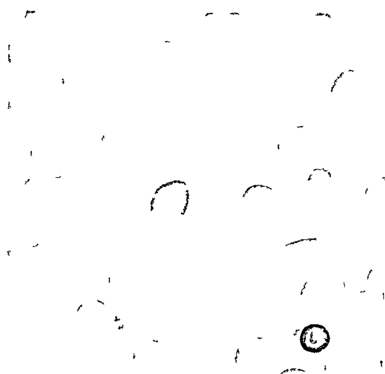
KEY TO PLATE 24

Mediterranean Anemia
Early Stage

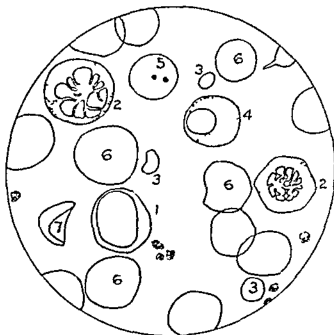
Some erythrocytes are of increased size but microcytic cells predominate, characteristically hemoglobin pigment is deficient and is often eccentrically placed A few stippled cells are seen nucleated erythrocytes are rare

1—Normoblast
2—Stippled cells
3—Macrocytic hypochromic cells
4—Poikilocytes

PLATE 24



x1200



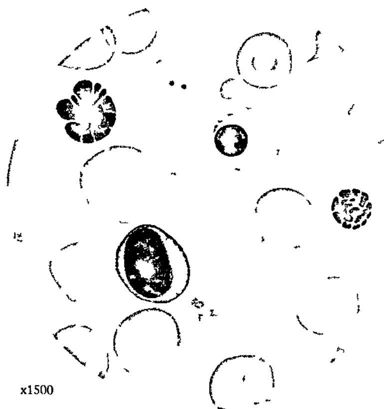
KEY TO PLATE 25

Mediterranean Anemia
Later Stage

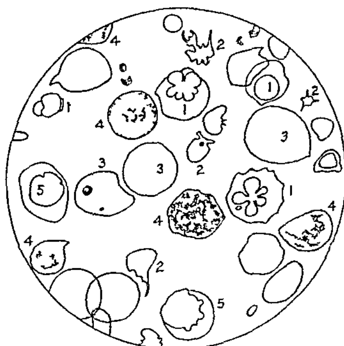
There is great variation in size and shape of the erythrocytes, with macrocytes predominating Hemoglobin deposits are often irregular, and the cells appear flatter and thinner than normal Nucleated erythrocytes are numerous

1—Megaloblast with large nucleus and deeply basophilic cytoplasm in which hemoglobin is beginning to appear
2—Erythroblasts with pyknotic nucleus breaking up, *cytoplasm shows basophilic stippling*
3—Microcytes
4—Normoblast with basophilic stippling
5—Polychromatophilic erythrocyte with Howell Jolly bodies
6—Macrocytes with deficient and irregular deposits of hemoglobin
7—Polychromatophilic erythrocyte with thin and folded over cytoplasm

PLATE 25



x1500



KEY TO PLATE 26

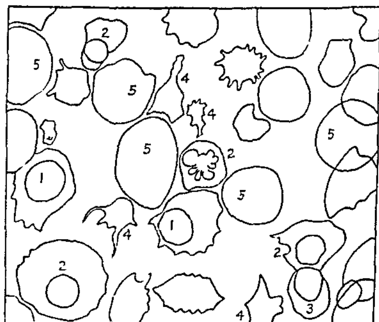
Mediterranean Anemia
Severe Form

There is great variation in size and shape of the erythrocytes and many large hypochromic cells with irregular deposits of hemoglobin are present. Nucleated erythrocytes are increased in number. Fragmentation of erythrocytes in the peripheral blood is a striking feature.

1—Normoblasts
2—Poikilocytes
3—Macrocytes with irregular hemoglobin deposits
4—Reticulocytes
5—Erythroblasts

PLATE 26





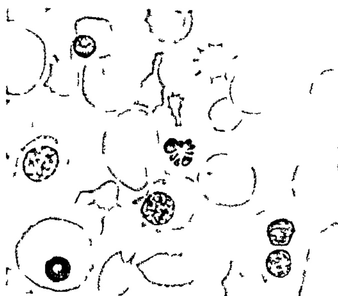
KEY TO PLATE 27

Mediterranean Anemia
Severe Form, after Splenectomy

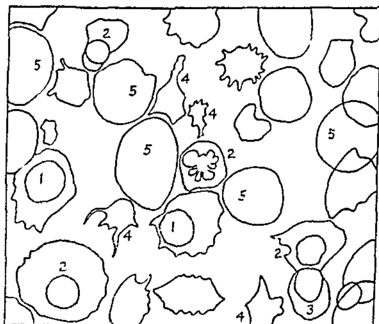
Erythrocytes show extreme variation is size, shape, and hemoglobin content with many nucleated cells of all ages, some stippled cells and much fragmentation Platelets are scarce

1—Erythroblasts
2—Normoblasts
3—Normoblast with basophilic stippling in cytoplasm
4—Poikilocytes
5—Macrocytes with irregular hemoglobin deposits

PLATE 27



x1500



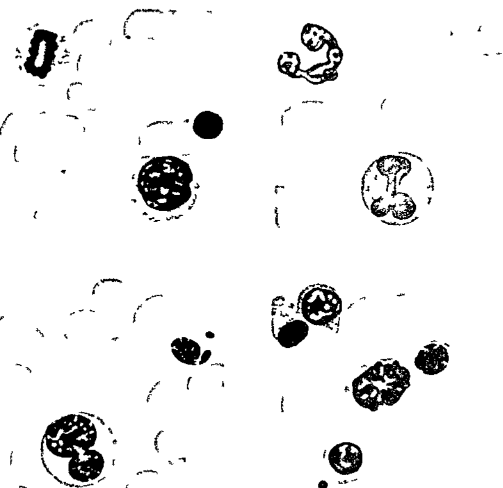
KEY TO PLATE 27

Mediterranean Anemia
Severe Form, after Splenectomy

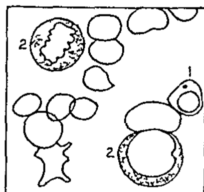
Erythrocytes show extreme variation is size shape, and hemoglobin content, with many nucleated cells of all ages, some stippled cells and much fragmentation Platelets are scarce

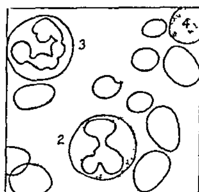
1—Erythroblasts
2—Normoblasts
3—Normoblast with basophilic stippling in cytoplasm
4—Poikilocytes
5—Macrocytes with irregular hemoglobin deposits

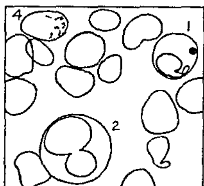
PLATE 28

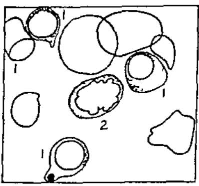


x1500









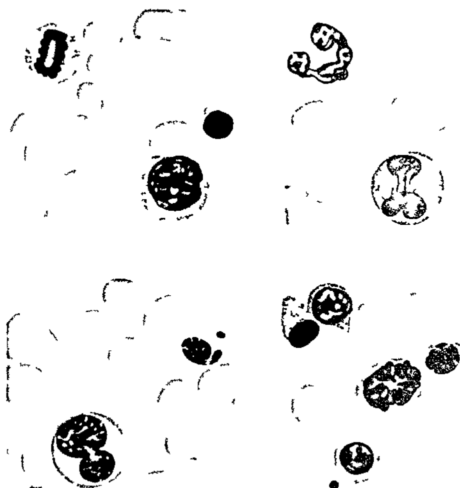
KEY TO PLATE 28

Mediterranean Amenia
Moderately Severe Form

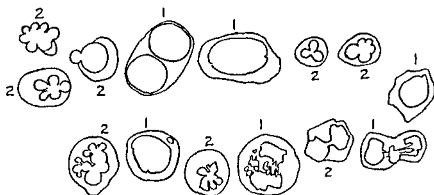
The erythrocytes vary markedly in size and shape, though microcytic cells predominate Hypochromia is severe Nucleated cells in all stages of development are present, and many cells have basophilic stippling

1—Normoblasts
2—Erythroblasts
3—Neutrophil
4—Stippled erythrocytes

PLATE 28



x1500



KEY TO PLATE 29

Mediterranean Anemia

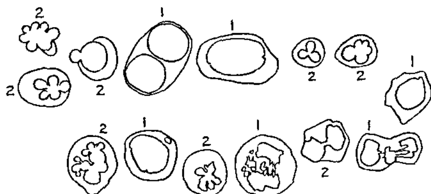
Selected nucleated red cells in various stages of maturation and division

1—Erythroblasts
2—Normoblasts

PLATE 29



x1500



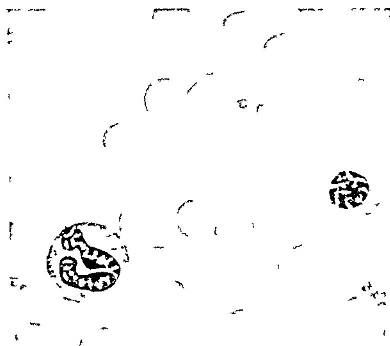
KEY TO PLATE 29

Mediterranean Anemia

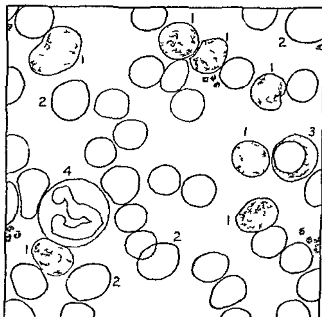
Selected nucleated red cells in various stages of maturation and division

1—Erythroblasts
2—Normoblasts

PLATE 30



x1500



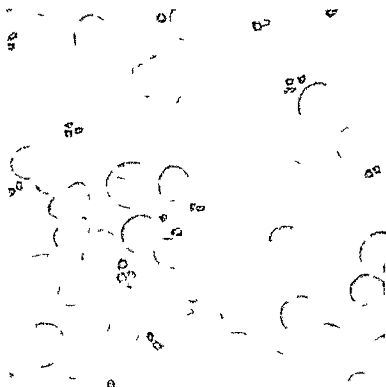
KEY TO PLATE 30

Acute Hemolytic Anemia

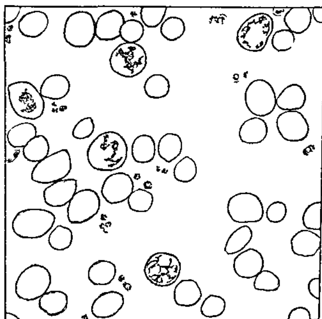
Erythrocytes tend to be large and well filled with hemoglobin Marked erythrogenesis is shown by the high percentage of reticulocytes principally large cells and some nucleated erythrocytes

1—Reticulocytes
2—Macrocytes
3—Nucleated erythrocyte
4—Neutrophil

PLATE 31



x1200

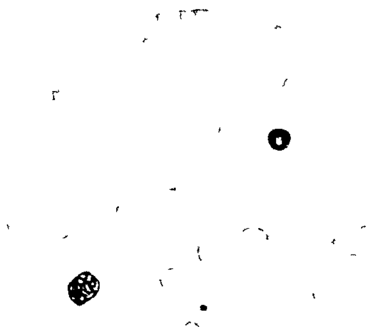


KEY TO PLATE 31

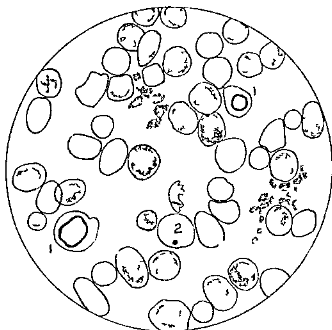
Congenital Hemolytic Anemia
Between Crises

Increased production of red cells is shown by the large number of reticulocytes Most adult cells are small and spherical in form without center depression—typical of the disease

PLATE 32



x1200



KEY TO PLATE 32

Congenital Hemolytic Anemia
During Crisis

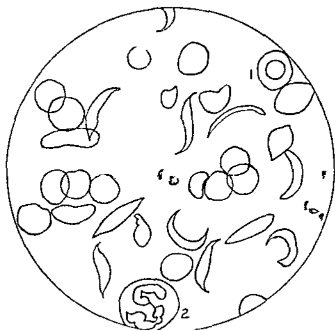
Active erythrogenesis is apparent, with reticulocytes making up more than half the total red cells There are occasional nucleated erythrocytes Platelets are increased

1—Normoblasts
2—Erythrocyte with Howell Jolly body

PLATE 33



x1200



KEY TO PLATE 33

Sickle Cell Anemia

Elongated sickle shaped erythrocytes typical of this condition are numerous An occasional nucleated erythrocyte is found

1—Normoblast
2—*Neutrophil*

PLATE 34

x1200



KEY TO PLATE 34

Sickle Cell Anemia

This is a fresh smear, unstained after half an hour in a hanging drop sealed preparation The erythrocytes show almost 100 per cent distortion to sickle forms

PLATE 34

x1200



KEY TO PLATE 34

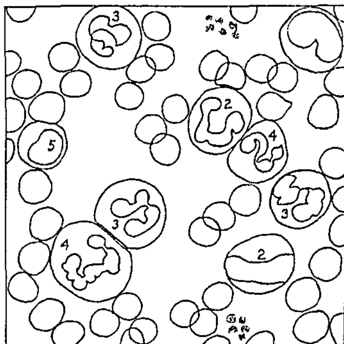
Sickle Cell Anemia

This is a fresh smear unstained after half an hour in a hanging drop sealed preparation The erythrocytes show almost 100 per cent distortion to sickle forms

PLATE 35



x1500



KEY TO PLATE 35

Neutrophils
Shift to the Left in Acute Infection

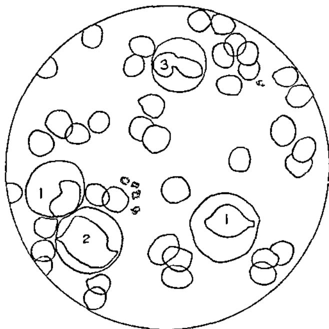
There is a marked increase in neutrophils, with young forms predominating

1—Late myelocyte with heavy granulation in cyto plasm, some granules overlaying the nucleus
2—Band forms of neutrophils
3—Two lobed neutrophils
4—Three lobed neutrophils
5—Medium lymphocyte

PLATE 35



x1500



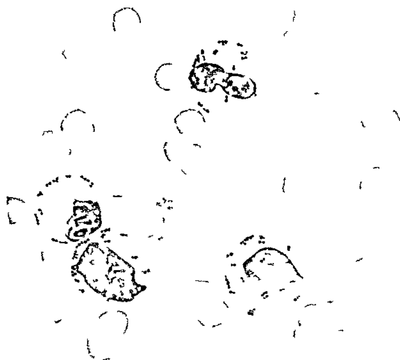
KEY TO PLATE 36

Neutrophils
Toxic Granulation in Prolonged Infection

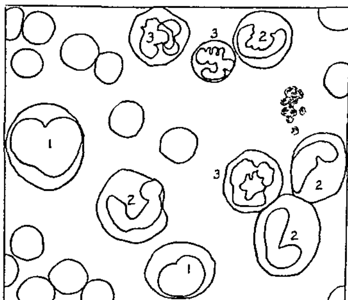
Neutrophils are present in large numbers, nuclei of most cells are band form or simply round, very few are lobulated Cytoplasm contains neutrophilic granulation and also larger dark purple or black granules—toxic granulation—an evidence of severe infection or toxemia

1—Young neutrophils with undivided nuclei and toxic granules
2—Myelocyte type C or late myelocyte, with toxic granules and vacuole of degeneration
3—Young or band form neutrophil with toxic granules

PLATE 36



x1500



KEY TO PLATE 37

Neutrophils
Acute Bacteremia

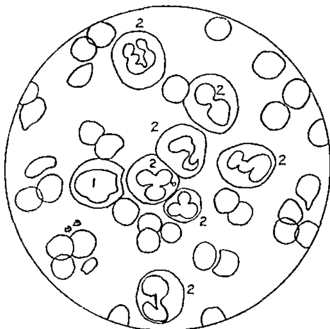
There is great increase in neutrophils Nuclei vary in shape from round to two and three lobed forms Cytoplasm is typically neutrophilic but contains many toxic granules as well as vacuoles of varying size at periphery

1—Young monocytes with basophilic cytoplasm
2—Young or band form neutrophils nuclei beginning to elongate and segment cytoplasm shows toxic granules and vacuoles
3—Lobulated forms of neutrophils with further maturation of nuclei cytoplasm shows toxic granules and occasional vacuoles

PLATE 37



x1500



KEY TO PLATE 38

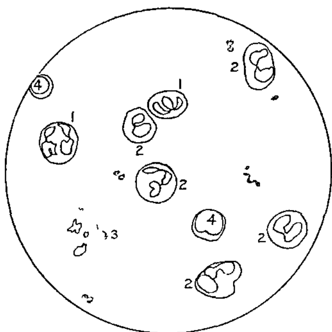
Neutrophils
Acute Toxemia Caused by Extensive
Severe Burn Toxic Granulation

Neutrophils are greatly increased in number Most of the nuclei are unlobulated (shift to the left) Cytoplasm has heavy toxic granulation and tendency to vacuolated degenerated forms

1—Late myelocyte with vacuolated cytoplasm
2—Neutrophils in different stages of maturation with toxic granules and vacuoles

PLATE 38





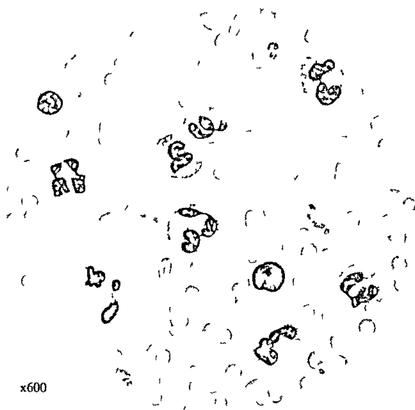
KEY TO PLATE 39

Eosinophils
Allergy

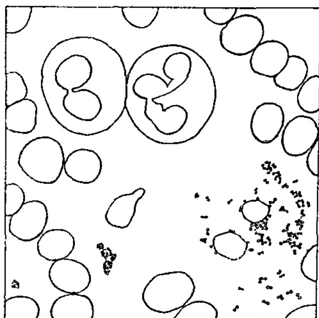
There is a striking increase in number of eosinophils These cells disintegrate easily in process of making smear preparation

1—Neutrophils
2—Eosinophils containing vacuoles
3—Disintegrated eosinophil
4—Lymphocytes

PLATE 39



x600

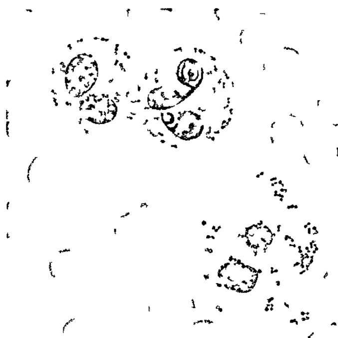


KEY TO PLATE 40

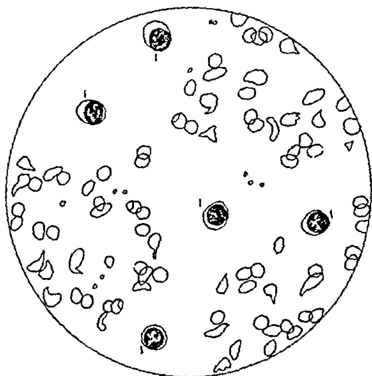
Eosinophils
Chronic Infection

Marked increase in number and percentage of eosinophils was the peculiar reaction of this individual to infection Nuclei are of typical polymorphonuclear type Cytoplasm contains sparser eosinophilic granulation and has tendency to disintegrate readily in process of making smear preparation

PLATE 40



x1500



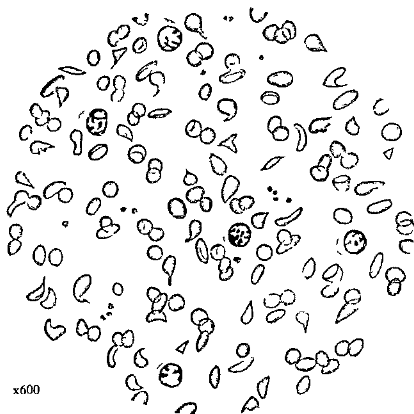
KEY TO PLATE 41

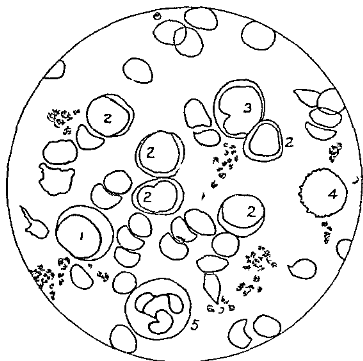
Lymphocytes
Chronic Iron Deficiency Anemia

Lymphocytes are increased in absolute number as well as *in percentage of total leukocytes* The *picture may suggest* leukemia but the lymphocytes are all of the mature type and the platelets usually reduced in leukemia in children are plentiful Erythrocytes show *marked microcytosis and* hypochromia and a moderate degree of poikilocytosis

1—Mature lymphocytes

PLATE 41





KEY TO PLATE 42

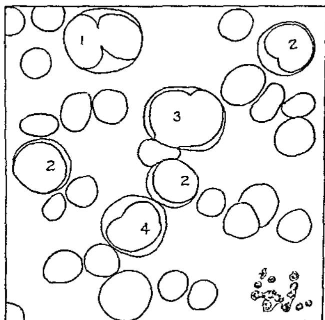
Lymphocytes
Pertussis

Lymphocytes are so numerous and make up such a large percentage of the total leukocytes that leukemia may be suggested, however they are mature forms Also platelets are numerous and erythrocytes are not reduced in number, in contrast to leukemia in childhood

1—Large lymphocyte
2—Small lymphocytes
3—Medium lymphocyte
4—Basophil
5—Neutrophil

PLATE 42





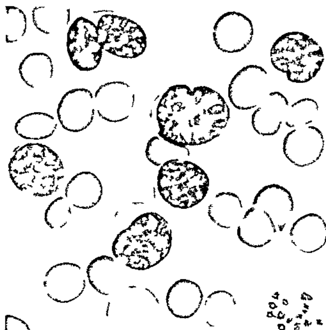
KEY TO PLATE 43

Lymphocytes
Severe Pertussis

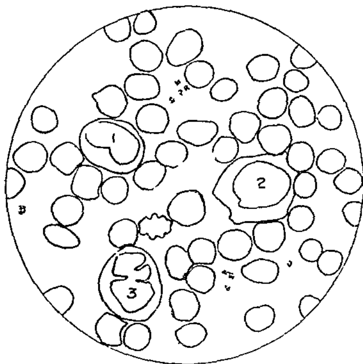
Lymphocytes are tremendously increased in both absolute number and percentage, occasionally reaching a level of 100 000 per cubic millimeter or more The mature character of the cells and the normal number of platelets and erythrocytes help to rule out leukemia in childhood

1—Large lympocyte with dividing nucleus
2—Small lymphocytes
3—Large lymphocyte
4—Medium lymphocyte

PLATE 43



x1500



KEY TO PLATE 44

Lymphocytes
Infectious Mononucleosis

There is an absolute as well as a relative increase in large lymphocytes that resemble monocytes in size However, the cells stain as do large lymphocytes with clear blue cytoplasm often azure granules and a condensed dark nucleus The cytoplasm seems very thin and is often compressed between and against red cells Occasionally small vacuoles are seen in the cytoplasm

1—*Large lymphocyte with many small vacuoles in* the cytoplasm

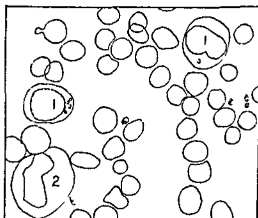
2—Large lymphocyte of the type characteristic of this condition

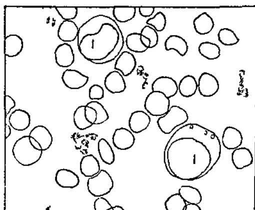
3—Large lymphocyte with granules and vacuoles in the cytoplasm

PLATE 44



x1200





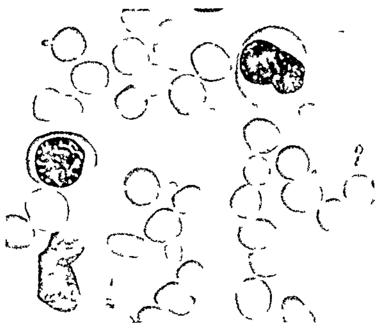
KEY TO PLATE 45

Lymphocytes
Infectious Mononucleosis

There is a marked increase in large mononuclear cells which by their typical light blue staining cytoplasm and dark purple staining nucleus may be identified as lymphocytes There is often a cart wheel arrangement of the chromatin in the nucleus The normal erythrocytes and platelets differentiate this from a leukemic blood picture

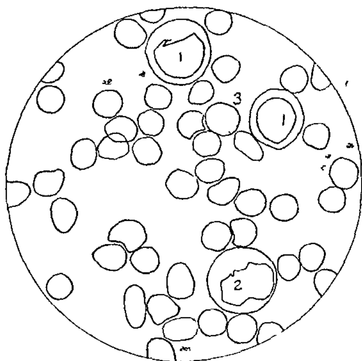
1—Lymphocytes typical of this condition
2—Normal monocyte

PLATE 45





x1200



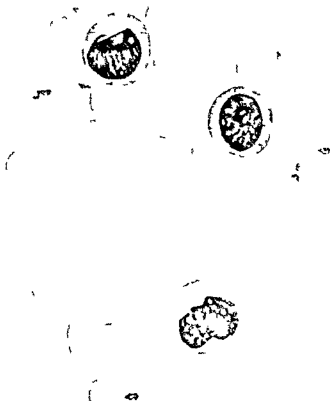
KEY TO PLATE 46

Lymphocytes
Infectious Mononucleosis

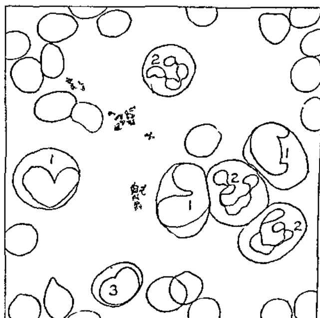
There is an increase in medium and large lymphocytes with clear light blue staining cytoplasm containing occasional vacuoles and fine granule The nucleus is dense and often has a cart wheel arrangement of the chromatin One erythrocyte in this field shows basophilic stippling

1—Medium lymphocytes
2—Large lymphocyte
3—Stippled red cell

PLATE 46



x1200



KEY TO PLATE 47

Monocytes
Acute Primary Tuberculosis

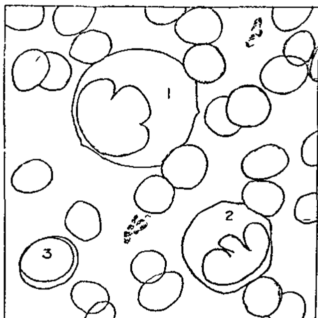
The total number of leukocytes is increased with absolute as well as relative increase in monocytes, mostly of the younger type and decrease in lymphocytes

1—Monocytes
2—Neutrophils
3—Lymphocyte

PLATE 47



x1500



KEY TO PLATE 48

Monocytes
Acute Primary Tuberculosis

Monocytes are increased in both number and percentage Giant monocytes of the type that Sabin named epithelioid or stimulated form are seen occasionally

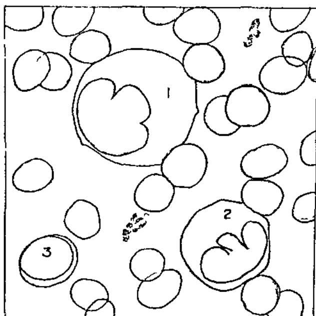
1—Giant monocyte, epithelioid form
2—Normal monocyte
3—Small lymphocyte

PLATE 18









KEY TO PLATE 48

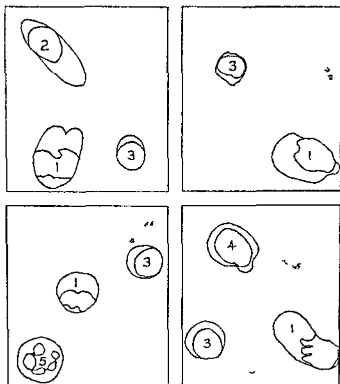
Monocytes
Acute Primary Tuberculosis

Monocytes are increased in both number and percentage Giant monocytes of the type that Sabin named epithelioid or stimulated form are seen occasionally

1—Giant monocyte, epithelioid form
2—Normal monocyte
3—Small lymphocyte



x1500



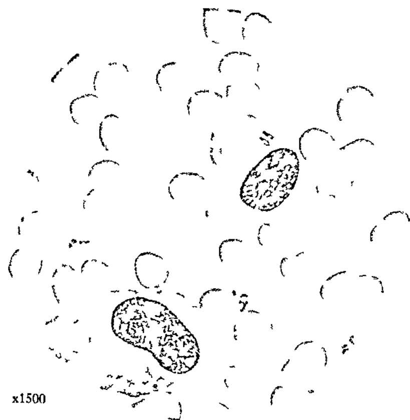
KEY TO PLATE 49

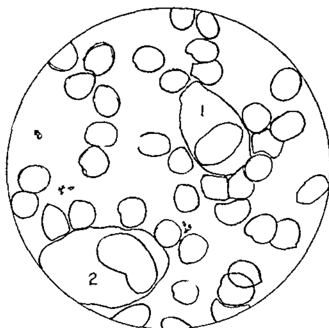
Monocytes
Lipoid Histiocytosis or Pick-Niemann s Disease

There is a relative increase in monocytes, many of which are of the phagocytic type These cells contain large numbers of vacuoles which by special staining reaction are found to be fat laden Lymphocytes and even neutrophils may contain similar vacuoles In this respect they reflect the findings in the tissues throughout the body

1—Monocytes with large vacuoles
2—Unvacuolated monocyte
3—Lymphocytes with small vacuoles
4—Large lymphocyte with vacuoles
5—Neutrophil with vacuoles

PLATE 50





KEY TO PLATE 50

Monocytes
Active Phagocytosis in Chronic Bacteremia

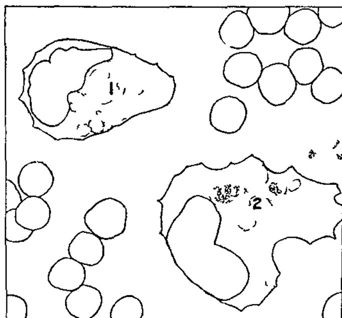
Giant monocytic cells with vacuoles containing recognizable ingested material make up 5 to 10 per cent of the leukocytes Such cells suggest active phagocytosis in the endothelial cells and in the peripheral circulation

1—Moderate sized monocyte with two vacuoles containing recognizable ingested material
2—Giant monocyte with three small vacuoles and a larger one containing ingested material

PLATE 51



x1500



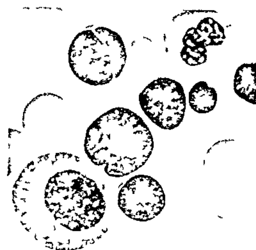
KEY TO PLATE 51

Monocytes
Extreme Phagocytosis in Bacterial Endocarditis

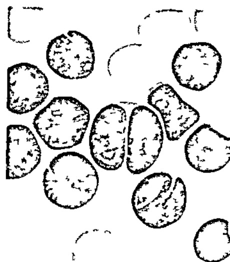
Monocytes of the type shown here may best be found in smears taken from a puncture of the lobe of the ear after massage They may make up only a small percentage of the leukocytes but are typical of the active phagocytosis seen in endocarditis

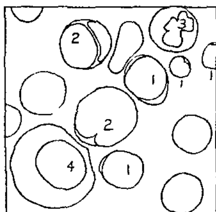
1—Giant monocyte containing recognizable neutrophil in the largest vacuole
2—Giant monocyte with phagocytized erythrocytes in two vacuoles

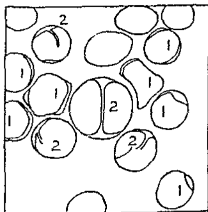
PLATE 52



x1500







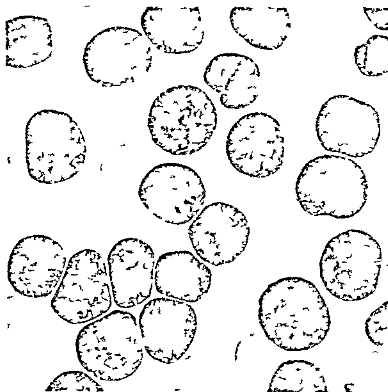
KEY TO PLATE 52

Acute Stem-Cell or Undifferentiated Cell-Type Leukemia

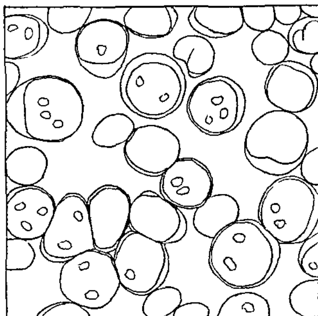
There are large numbers of leukocytes of various sizes with dividing nuclei scant cytoplasm and occasional nucleoli The typical basophilic cytoplasm and the undifferentiated type of nucleus suggests that the cell is a stem cell Platelets are absent The red cells show no apparent alteration

1—Immature or stem cells
2—Immature or stem cells with dividing nuclei
3—Neutrophil with unlobulated nucleus
4—Eosinophilic myelocyte with unlobulated nucleus

PLATE 53



x1500

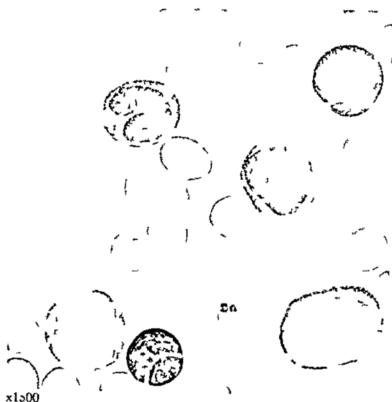


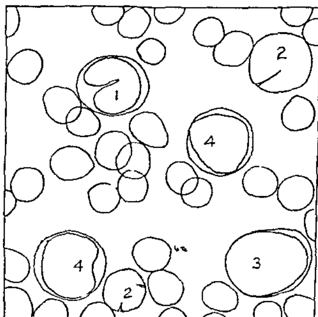
KEY TO PLATE 53

Acute Myeloblastic Leukemia

The field is crowded with leukocytes containing a single nucleus and cytoplasm that is scant and typically basophilic Many of the nuclei contain lighter stained punched out areas which are nucleoli Although the cells are very immature and close to stem cells the characteristics of the nucleus and the multiple nucleoli found in each suggest that they are myelo blasts Platelets are rare Erythrocytes are normal in appearance

PLATE 54





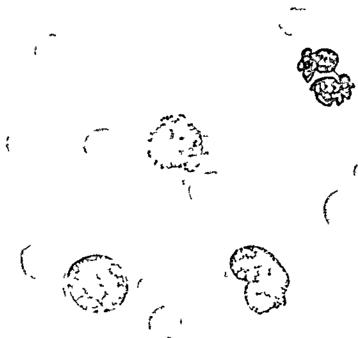
KEY TO PLATE 54

Acute Myeloid Leukemia

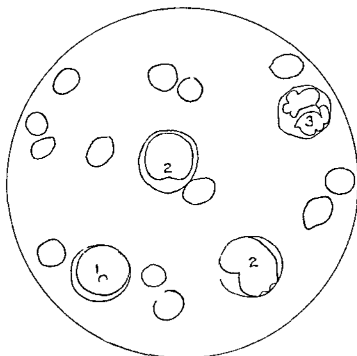
The predominating cell is of the large mononuclear variety with typically blue staining scant cytoplasm and heavy dark blue granules at the periphery The nucleus of this immature cell contains nucleoli Occasionally a nucleus is found in partial division Platelets are rare Erythrocytes are normal in appearance occasional stippled red cells may be found

1—Myelocyte early form
2—*Myeloblasts with dividing nuclei*
3—Myeloblast with heavy cytoplasmic granulation
4—Myeloblasts with nucleoli and heavy cytoplasmic granulation

PLATE 55



x1500



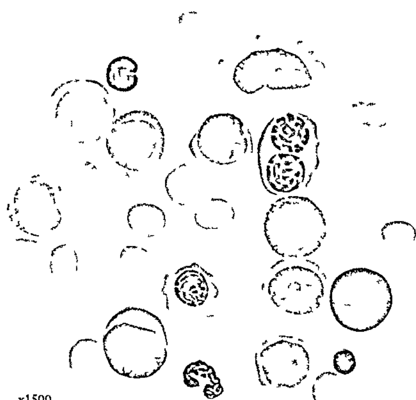
KEY TO PLATE 55

Acute Myeloid Leukemia

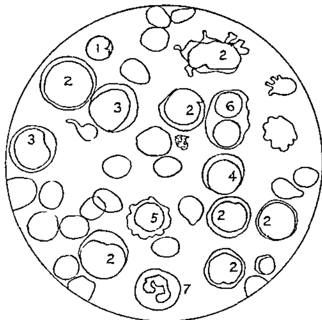
Although the number of leukocytes is not increased, there is a high percentage of immature myeloid forms these are mostly myelocytes but some are myeloblasts Platelets are scarce Erythrocytes are normal in appearance

1—Myeloblast with nucleoli
2—Myelocytes, early forms
3—Neutrophil

PLATE 56



x1500



KEY TO PLATE 56

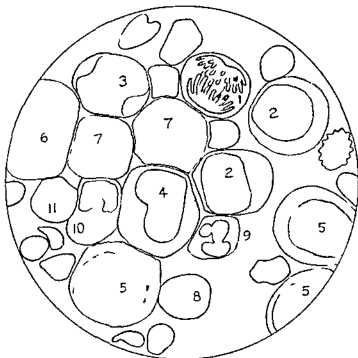
Subacute Myeloid Leukemia

Myeloid cells are not greatly increased either absolutely or relatively, but a large percentage of them are mononuclear cells with scant basophilic cytoplasm and nucleoli in the nucleus Myelocytes in all stages of development are seen Platelets are scarce Erythrocytes are normal in appearance but there are many nucleated cells which suggests bone marrow invasion or irritation

1—Small myeloblast with dividing nucleus
2—Myeloblasts with scant basophilic cytoplasm and nucleoli in the nucleus
3—Early myelocytes with slight amount of granulation in the cytoplasm and overlying the nucleus
4—Myelocyte later stage with heavy granulation crowded into the cell
5—Nucleated erythrocyte
6—Nucleated erythrocyte with dividing nucleus
7—Neutrophil

PLATE 57


x1800



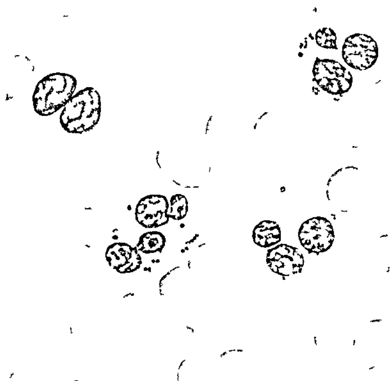
KEY TO PLATE 57

Chronic Myeloid Leukemia, Terminal Stage

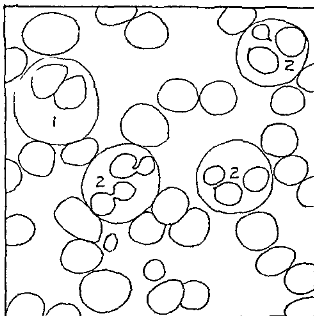
All types of myeloid cells that are ordinarily found in the bone marrow flood the peripheral circulation in the terminal stages of chronic leukemia Myeloblasts with nucleoli and basophilic cytoplasm, cells with mitotic figures, myelocytes with heavy granulation as well as more mature myeloid cells abound Platelets are rare Erythrocytes appear normal This picture is rarely seen in childhood

1—Mitotic figure
2—Myeloblasts with nucleoli
3—Myeloblast with nucleoli and vacuoles in the cytoplasm
4—Myeloblast with nucleoli in the nucleus and a large amount of cytoplasm
5—Myelocytes early forms
6—Myelocyte giant early form with basophilic granulation
7—Myelocytes, early form with basophilic granulation
8—Myelocyte late form
9—Neutrophil
10—Eosinophil
11—Basophil

PLATE 58



x1500



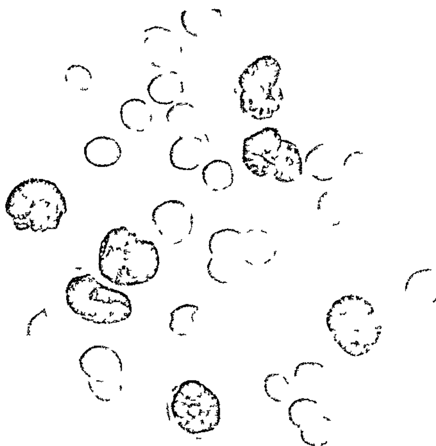
KEY TO PLATE 58

Chronic Eosinophilic Leukemia

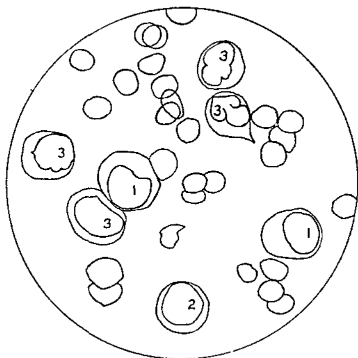
This is a rare form of leukemia There is a marked increase in polymorphonuclear cells with light blue cytoplasm containing sparse, typically eosinophilic granules Platelets are few Erythrocytes may be normal, although in this instance they tend to be macrocytic

1—Eosinophil with only three or four granules
2—Eosinophils with twenty to thirty granules in each cell in contrast to the hundreds usually found

PLATE 59



x1500



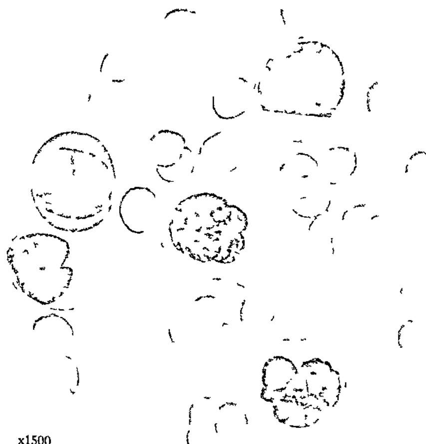
KEY TO PLATE 59

Acute Monocytic Leukemia

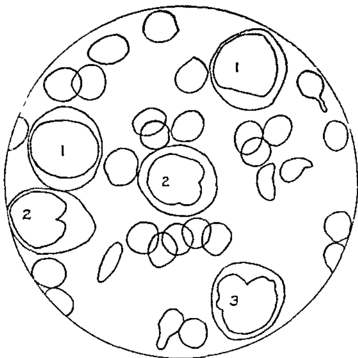
There is an increase in the total number of white cells with mononuclear types predominating In these cells the nucleus is frequently folded on itself and contains only occasional nucleoli, the cytoplasm is bluish gray and moderate in amount Platelets are rare Erythrocytes are normal in appearance

1—Immature monocytes probably monoblasts
2—Cell with nucleoli in the nucleus
3—Cells with piled up, folded nuclei

PLATE 60



x1500



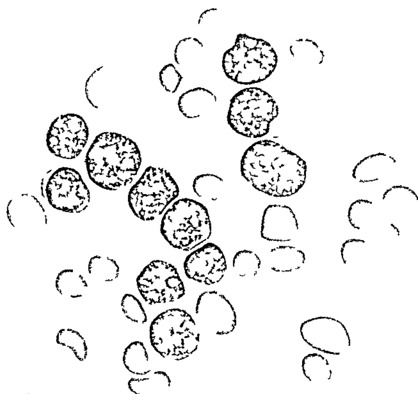
KEY TO PLATE 60

Subacute Monocytic Leukemia

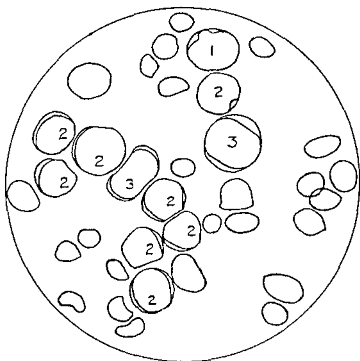
Leukocytes are increased and are predominantly mono cytic with large amounts of cytoplasm grayish blue in staining reaction containing fine granulation An occasional nucleus is divided and folded over on itself, nucleoli are fre quently seen Platelets are rare Erythrocytes appear normal

1—Immature monocytes probably monoblasts
2—Cells with nucleoli and dividing or folded nucleus
3—Cell with nucleoli in the nucleus and vacuoles in the cytoplasm

PLATE 61



x1500



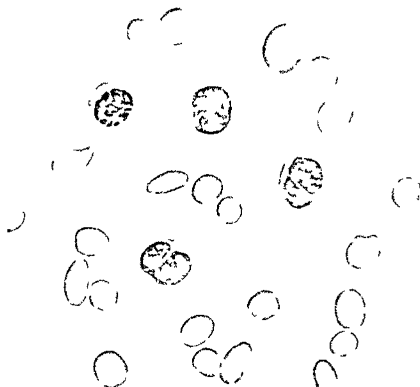
KEY TO PLATE 61

Acute Lymphoblastic Leukemia

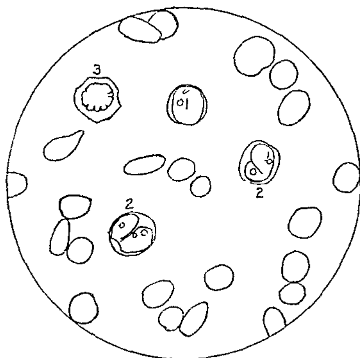
There are large numbers of mononuclear cells generally of small size, with scant, deeply basophilic cytoplasm The nuclei contain some lighter staining punched out holes which are nucleoli It is difficult to differentiate these cells (lymphoblasts) from the comparable immature cells of the myeloid series (myeloblasts) Platelets are rare Erythrocytes vary somewhat in size and shape

1—Lymphoblast with irregular nucleus
2—Lymphoblasts with scant cytoplasm
3—Lymphoblasts with small amount of cytoplasm

PLATE 62



x1200



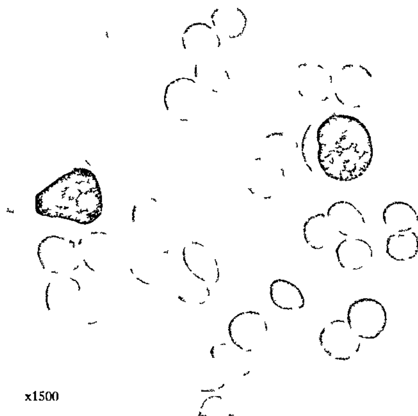
KEY TO PLATE 62

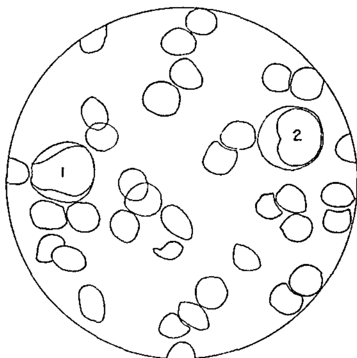
Subacute Lymphoid Leukemia

The predominating white cells are of the small lymphoid type, often with dividing nucleus and nucleoli readily visible Platelets are absent Occasional nucleated erythrocytes are seen

1—Lymphoblast with nucleoli and single round nucleus and scant basophilic cytoplasm
2—Lymphoblasts with dividing nucleus, nucleoli, and moderate amount of basophilic cytoplasm
3—Nucleated erythrocyte

PLATE 63





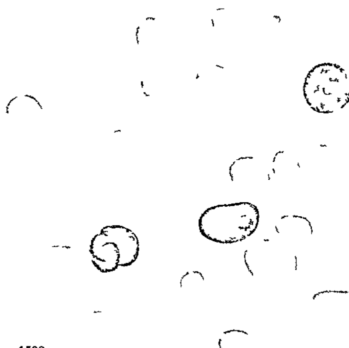
KEY TO PLATE 63

Subacute Lymphoid Leukemia, Leukopenic Stage

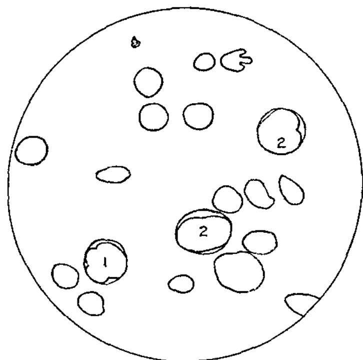
There are few white cells but they are uniformly of an undifferentiated lymphoid type with a small amount of basophilic cytoplasm and a nucleus containing nucleoli Platelets are absent

1—Lymphoblast with moderate amount of cytoplasm and a nucleolus in the nucleus
2—Lymphoblast with moderate amount of cytoplasm and several nucleoli in the nucleus

PLATE 64



x1500



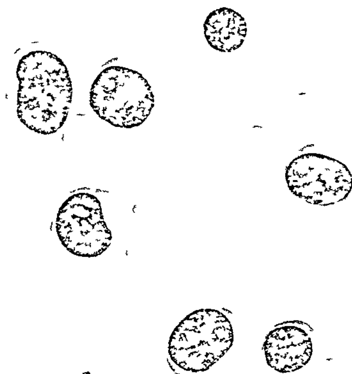
KEY TO PLATE 64

Subacute Lymphoid Leukemia, Leukopenic Stage

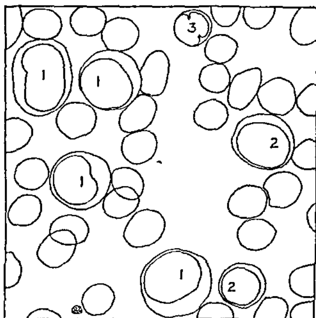
The level of leukocytes is low and the majority of cells are of the lymphoid type with scant basophilic cytoplasm and *nucleoli in the nucleus, some nuclei show amitotic division* Platelets are rare Erythrocytes vary slightly in size and shape

1—Immature lymphoid cell with dividing nucleus and scant cytoplasm
2—Immature lymphoid cells with nucleoli in the nucleus

PLATE 65



x1500



KEY TO PLATE 65

Chronic Lymphoid Leukemia

The leukocytes are increased in number and are predominantly of a medium to large lymphoid type with scant to moderate basophilic cytoplasm. The nucleus contains nucleoli and is often seen in process of division. Platelets are scarce. Erythrocytes appear normal.

1—Lymphoblasts with nucleoli in the nucleus and a moderate amount of basophilic cytoplasm
2—Small lymphoblasts with nucleoli in the nucleus and scant basophilic cytoplasm
3—Lymphoblast with dividing nucleus

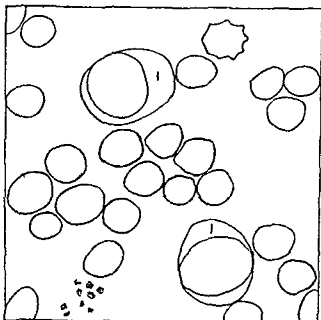
PLATE 66







x1500



KEY TO PLATE 66

Chronic Lymphoid Leukemia, Plasma Cell Type

Although the leukocyte level is not greatly increased, the cells are predominantly of the large lymphoid type, with a moderate amount of deeply basophilic cytoplasm having a broken appearance In the cytoplasm there is a clear, light-blue staining area adjacent to the nucleus The nucleus shows heavy chromatin stain sometimes arranged in characteristic cart wheel fashion Platelets may not be reduced as much as in other kinds of leukemia except terminally Erythrocytes appear normal

1—Lymphoid cells of the typical plasma cell variety

PLATE 67









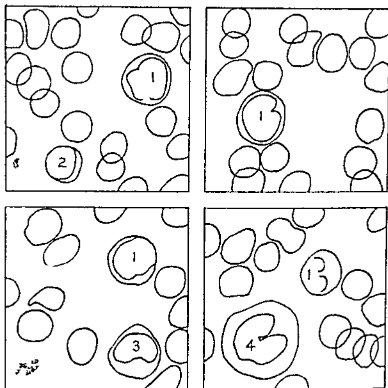








x1500



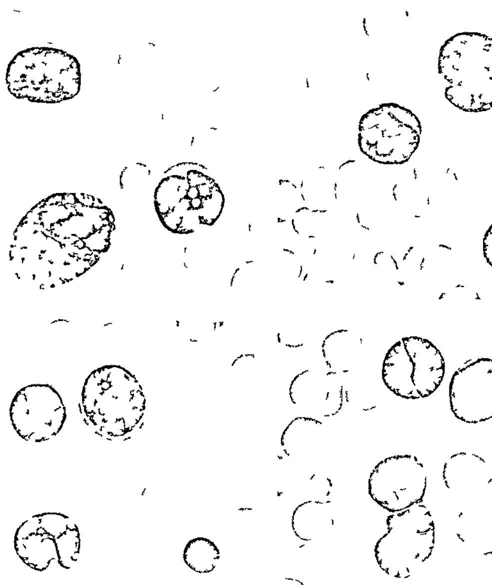
KEY TO PLATE 67

Early Subacute Lymphoid Leukemia, Leukopenic Stage

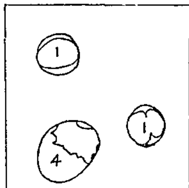
The total number of leukocytes is low and less than 10 per cent of them are immature lymphoid cells with only moderate amount of basophilic cytoplasm The nucleus is often in a state of division or folded over on itself Nucleoli are present in all these lymphoblasts Platelets are normal in number Erythrocytes are unchanged in appearance

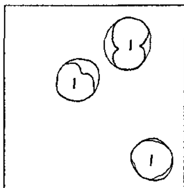
1—Lymphoblasts with dividing nucleus scant basophilic cytoplasm, and nucleoli
2—Normal mature or small lymphocyte
3—Large lymphocyte
4—Normal monocyte

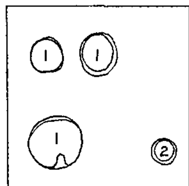
PLATE 68

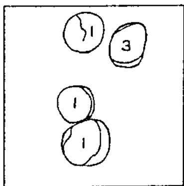


x1500









KEY TO PLATE 68

Subacute Lymphoid Leukemia Terminal Leukocytosis

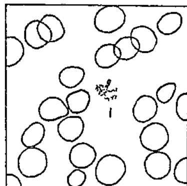
This field is from the same case as Plate 67 The leukocytes are much more numerous and the predominating form is the lymphoblast, in some instances with basophilic cytoplasm, often scant in amount and dividing nucleus containing nucleoli An occasional myelocyte is seen Platelets are absent Erythrocytes appear normal

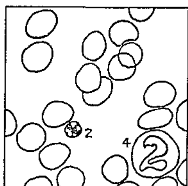
1—Lymphoblasts with scant basophilic cytoplasm and nucleoli in the nucleus
2—Small lymphocyte
3—Medium lymphocyte
4—Myelocyte early stage

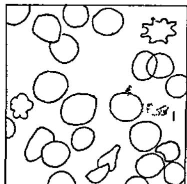
PLATE 69

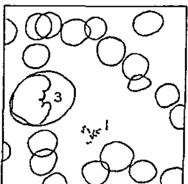


x1500









KEY TO PLATE 69

Chronic Thrombocytopenia Purpura Hemorrhagica

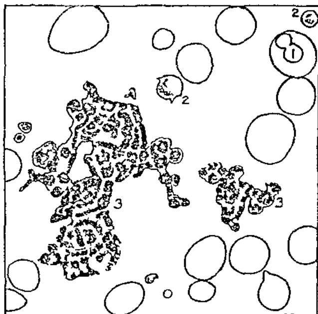
Erythrocytes and leukocytes are abundant, but platelets are extremely rare and those found are generally much larger than normal They do not stain distinctly and are irregular in shape

1—Giant platelets
2—Medium platelet
3—Monocyte
4—Neutrophil

PLATE 70



x1500



KEY TO PLATE 70

Thrombocytosis following Splenectomy

Masses of platelets and single platelets are found in abundance they are normal in staining reaction Occasionally erythrocytes may show some variation in size and shape, and nucleated cells are seen This type of platelet increase usually appears in the second to third week following removal of the spleen

1—Normoblast
2—Giant single platelets
3—Masses of platelets

Index